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BLOOD VOLUME AND HEMATOLOGIC STUDIES IN PREGNANCY AND THE PUERPERIUM*†

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THIS investigation was initiated in an effort to clarify the conflicting results which exist regarding the hemodilution in pregnancy, to attempt to correlate the hematologic picture with this hydremia, both ante partum and post partum, and to establish normal hematologic values for pregnancy, a deviation from which might permit the diagnosis of an early pathologic anemia. The literature varies with regard to the normal hematologic findings in pregnancy.

Review of the Literature

Opinion differs concerning the effects of economic status^{1, 2} and parity^{2, 3, 4} upon the hemoglobin levels in pregnancy. The observation of Fullerton that hemoglobin values fell with increasing age during the reproductive years may explain the frequency of anemia in the older age group.^{3, 4} Other mentioned factors are decreased gastric acidity, seasonal variations, rapidly succeeding pregnancies, and other influences, such as dietary deficiencies and complicating diseases which affect the hemopoietic system.

It is difficult to compare the results of the many studies of the hemoglobin in pregnancy because of the great variation in methods of study and reporting. Whenever possible in this review, hemoglobin values have been converted to grams per cent.

The importance of serial studies was emphasized by Dieckmann and Wegner, McGeorge, Cohen and Thompson, Boycott, Meyer-Wedell, Wolff and Limarzi, and Hoch and Marraek.^{2, 8, 9, 12, 17, 18}

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There is general accord that the hemoglobin falls during pregnancy,¹⁻¹⁹ but considerable controversy exists regarding the extent and time of this fall. The reported minimal levels vary from 9.1 to 12.53 Gm. per cent (Table I). From these data it is impossible to determine the maximum fall of hemoglobin in normal pregnancy. Most investigators found that the hemoglobin level reached its lowest values in the last trimester. A rise was variably noted in the eighth, and ninth,⁹ and the tenth lunar months.^{2, 5, 6, 8, 10-12, 15, 17} Absence of increase of hemoglobin during late pregnancy has been reported.³ Although the hemoglobin concentration decreases during pregnancy, Dieckmann and Wegner⁸ found an increase of the average total hemoglobin mass of 13 per cent, which compares favorably with the 12 per cent increase observed more recently by Roscoe and Donaldson.¹⁹

TABLE I. MINIMAL HEMOGLOBIN VALUES IN PREGNANCY

YEAR	AUTHORITY	CASES	PERCENTAGE OF CASES WITH HGB LESS THAN			
			11 GM. %	10.36 GM. %	10.00 GM. %	9.66 GM. %
1930	Bland ⁶	1,000	58.6%			
1935	McGeorge ⁹	94		17%		
1936	Boycott ²	222	22%			
1936	Adair et al. ¹	7,835			11.6%	
1937	Reid and Mackintosh ³⁴	1,108	54%		10.2%	
1941	Kay and Alston ¹⁶	2,005 (1939) 814 (1941)				5.3% 39 %
1943	Meyer-Wedell ¹⁷	94				46.8%
1944	Fullerton et al. ³⁵	819 (1935) (1936)				17.5% 3.9%
1948	Sadovsky ⁴	78		2.56%		

The hemoglobin increases post partum.^{5, 6, 9, 12, 17, 18} However, the time post partum at which the normal nonpregnant hemoglobin concentration is attained varies with different authors from 10 days to 6 months.^{5, 7, 9, 10, 12, 15, 17} Some observed a decrease and others observed an increase immediately after delivery. A few noted a constant trend in hemoglobin fluctuation in the early puerperium.^{5, 15}

To summarize: The hemoglobin concentration falls during pregnancy, reaches its minimal level in the last trimester, and increases slightly to term. An increase of the total hemoglobin mass has been observed during pregnancy. There is no satisfactory agreement as regards the time post partum at which the hemoglobin concentration returns to the nonpregnant normal.

The red cell count parallels the changes of hemoglobin concentration in pregnancy. It progressively decreases to a minimal level of 3.7 to 4.15 million in the last trimester.^{1, 5, 7, 8, 14, 15, 17-20} It has been shown to rise in the ninth¹⁷ and tenth lunar months,^{5, 15} and to continue to increase after delivery.^{5, 6-8, 18, 19} The time post partum at which nonpregnant normal counts are attained varied from the seventh day to the sixth week.¹⁷⁻²⁰ The red cell count showed a variable pattern immediately after delivery.^{5, 7, 15}

To summarize: The red cell count decreases in pregnancy and increases slightly to term. Although it is generally accepted that it returns to the nonpregnant normal earlier after delivery than the hemoglobin concentration, the exact time of this recovery is unsettled.

There is ample evidence that the hematocrit falls during pregnancy^{1, 5, 8, 11, 12, 15, 18, 19, 21} to minimum values ranging from 28.1 per cent to 38.5 per cent in the third trimester,^{1, 8, 11, 15, 18} and increases slightly in the last lunar month.^{5, 11, 12, 15, 21}

The hematocrit recovers post partum.^{5, 12, 15, 18, 21} A varied pattern has been reported during the first few postpartum days.^{5, 9, 15} Values ranging from 36.6 per cent to 42.7 per cent have been reported 7 to 14 days post partum^{12, 15} and 37 per cent to 44 per cent by 30 to 60 days post partum.^{11, 18, 21}

To summarize: The hematocrit falls to a minimal level in the last trimester of the pregnancy and then rises slightly during the last lunar month. Most investigators found a rapid recovery of the hematocrit to normal non-pregnant levels by the seventh to fourteenth days post partum.

Varied reticulocyte counts have been reported during pregnancy. Most observers found no change,^{2, 15, 17, 18} although others noted a slight increase.^{11, 14} Labate¹⁵ found the reticulocytes to be normal in the first 10 days post partum.

Most authors agree that the color index is normal during pregnancy, confinement,^{2, 17, 18} and the puerperium.

Wolff and Limarzi computed the mean corpuscular volume and found it to be within the normal nonpregnant range.¹⁸ Labate¹⁵ noted slightly increased values from the thirty-eighth week to the tenth postpartum day.

Both the mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration have been found to be within the nonpregnant normal range both ante partum and post partum.^{15, 18, 22} Labate,^{15, 22} however, noted a macrocytosis in many cases, with lowered mean corpuscular hemoglobin concentration especially during the last 3 lunar months and the first 10 days post partum.

Normal nonpregnant leucocyte counts have been reported in pregnancy,^{7, 14, 18, 19, 23} although most authors stressed the development of a leucocytosis, due to a neutrophilia with a shift to the left of neutrophiles, in the later months of pregnancy^{7, 17, 18} and in labor.²³ The time post partum at which the leucocytes return to the nonpregnant normal varied from a few days to 6 weeks. Wolff and Limarzi found increased granulopoiesis of the bone marrow both ante partum and post partum.

To summarize: The white count is normal or slightly elevated during the first two trimesters. A leucocytosis is present during the last trimester which increases with approaching delivery. The leucocytes rapidly return to the nonpregnant normal in the puerperium. The leucocytosis is characterized by neutrophilia with a shift to the left of neutrophiles.

An increase of the uncorrected sedimentation rate has been noted during pregnancy.^{11, 18, 20, 24-26} This increase becomes apparent in the second trimester and reaches its maximum value in the third trimester. A rapid decrease of the sedimentation rate with return to the nonpregnant normal by one month post partum was observed by most authors.

Material and Method of Study

Serial observations were limited to 15 pregnant women due to the involved nature of the study. One developed pre-eclampsia and was discarded from the normal group. One patient was delivered by cesarean section because of central placenta previa and another suffered a postpartum hemorrhage; both were excluded from the normal postpartum group.

Of the fourteen normal antepartum patients two were primiparas and twelve were multiparas; ages ranged from 20 to 38 years, average 27 years. Of the twelve normal postpartum patients, one was a primipara and ten were multiparas, aged 20 to 38 years, average 27.8.

All patients attended the outpatient department of the Royal Victoria Hospital.

Each patient was examined every calendar month, although the last two antepartum determinations were timed to coincide with the ninth and tenth

lunar months. The last antepartum examination was performed as close to the onset of labor as possible. For the final computation the times of the visits in each pregnancy were calculated back in calendar months from the time of delivery except for the two cesarean section cases in which the estimated due date was utilized.

Routine studies were performed on the seventh to ninth and thirtieth postpartum days and, when conditions permitted, the second, the third to fourth, the fourteenth to sixteenth, and, finally, on the sixtieth day post partum.

It seemed advisable to determine whether the hematologic findings of this small group of patients were well within the normal range for pregnancy. Patients delivered in the maternity wing of the Royal Victoria Hospital are sent routinely to the Bessborough Laboratory one or more times ante partum for hemoglobin, red cell, and white cell determinations. Red cell and/or hemoglobin determinations are performed on each of these patients during the first week post partum. The median and the second and third quartiles of the observation made from July to December in the years 1946 (500 cases), 1947 (375 cases), and 1948 (400 cases) were computed and plotted in graph form. Although more of these determinations were performed during the early than during the late months of pregnancy, all the graphed results are statistically significant.

Technique

Blood volumes were determined by the method of Gibson and Evans²⁷ as adapted by Gibson and Evelyn²⁸ for the Evelyn photoelectric microcolorimeter.

All studies were performed with the patient in a basal state. Approximately 2.5 c.c. of Evans Blue dye (T-1824) were drawn into a sterile 10 c.c. syringe, and the dye, syringe, and needle (plugged with paraffin wax to prevent loss of dye) were weighed. At the bedside 5 c.c. of blood were collected in a corked centrifuge tube as the dye-free sample, and 5 c.c. were collected for hematologic study in a bottle containing 6 mg. of ammonium oxalate and 4 mg. of potassium oxalate. The dye was then slowly introduced through the same needle; syringe and needle were then withdrawn and the plunger of the syringe was given a quick pull to clear the needle of dye. The original needle was then attached to the syringe for reweighing. Early in the investigation three ten-minute dyed samples were obtained; later, the number was reduced to two.

The dye-free syringe and needle were weighed and the relative dye concentrations of the serum were determined. These were transferred to logarithmic expressions ($L = 2 - \log G$), which in turn were extrapolated back to zero time on semilogarithmic paper.^{29, 30} This extrapolated value was applied to a standard curve to obtain the concentration of dye (in gammas) in 1 c.c. of serum. The standard curve was computed with each new lot of dye using dilutions of the dye with distilled water.³⁶ As a check against this method of preparing the standard, one lot of dye was also standardized using dilutions of the dye with plasma. The difference was negligible over the range used. After correction of the hematocrit with Gregersen's factor ($\times 0.96$), the total blood and red cell volumes were computed.³¹

The hematologic determinations were performed with National Bureau of Standards pipettes and carefully standardized equipment and were often determined in duplicate. The hemoglobin concentration was determined with the Evelyn photoelectric colorimeter, 15.6 Gm. per cent being equivalent to 100 per cent. Hematocrit and sedimentation rate were performed by the method of Wintrobe. Platelets and reticulocytes were counted by Dameshek's

method and the platelets were also counted by the direct method using 3.5 per cent sodium citrate as diluent. Leucocyte differential smears were made by the cover-slip method and stained with Jenner-Giemsa.

Results

Antepartum and Postpartum Blood Volume Studies.—

Various authors have reported blood volume determinations in terms of total volume, volume per kilogram, and volume per square meter of body surface. Although in this study the results were plotted by all three methods, only the chart showing the changes in total volume is presented (Fig. 1). The pattern of the curves of blood volume changes were identical when expressed by all three methods.

In the nonpregnant state blood volume is most accurate when calculated in terms of surface area. This is not true in pregnancy because the dye T-1824 does not cross the placental barrier.²¹

The total blood volume of all 14 patients increased during pregnancy due principally to a rise of plasma volume. The initial total blood and plasma volumes were not greater than the postpartum values, in contrast to the findings of Caton and associates. The average values plateaued at the seventh month and decreased slightly in the eighth month in 3 patients and in the ninth month in 10 patients.

The total blood volumes of the first few patients observed on the eighth postpartum day were within the normal nonpregnant range^{13, 19, 32}; thereafter the blood volumes eight days after delivery were used as the standard for the nonpregnant normal of this series. Subsequently other patients were followed on the second, fourth, sixteenth, thirtieth, and sixtieth days post partum. The similar values on the second, fourth, and eighth postpartum days suggest that the blood volume returns to the nonpregnant normal shortly after delivery, although the small number of cases studied on the second and fourth days prohibit a definite conclusion.

In this series the averages of the initial antepartum and the eighth, thirtieth, and sixtieth days post partum blood volumes closely approximated the nonpregnant average of 2,660 ml. per square meter and 74.5 ml. per kilogram reported by Roscoe and Donaldson.

A Comparison With Blood Volume Studies from the Literature.—

The literature is too voluminous to detail in this paper. The findings of those authors who used the dye T-1824 are compared in Tables II, III, and IV with the results of this series. Except for the report of Thompson and co-workers, these publications appeared after our study was initiated. The investigations completed by 1934 were tabled by Dieckmann and Wegner.³³ McLennan and Thouin³² reviewed the studies reported from 1934 to 1948.

The ninth and tenth lunar months and the postpartum period were selected for tabular comparison because marked changes occur at these times.

The nonpregnant normal blood volumes for the patients of this series and those of Caton and associates were the average values observed after stabilization of the blood volume in the puerperium. Other investigators determined their normals from a series of normal nonpregnant women selected at random. The validity of the latter method may be questioned because of the tremendous fluctuation between individual patients and different series.

The percentage increases noted in Tables II and III represent the increase in total blood, plasma and red cell volumes above each author's normal nonpregnant standard.

Ninth Lunar Month (Table II).—

The total volumes of this series were greater in the ninth lunar month than those of Thomson and collaborators, although the percentage increase

TABLE II. COMPARISON OF BLOOD VOLUME STUDIES IN PREGNANCY
NINTH LUNAR MONTH

AUTHORITY	NO. OF CASES	METHOD	NONPREGNANT STANDARD	TBV/ C.C.	TBV/ KG.	TBV/ SQ. M.	PV/ C.C.	PV/ KG.	PV/ SQ. M.	RBCV/ C.C.	RBCV/ KG.	RBCV/ SQ. M.
Thomson et al. ¹³	14	Gibson and Evans	No. of cases = 28 TBV = 3,920 (3,110-4,870)	5,705 >45.5%	90 >25.2%		3,913 >65%	61.7		1,805 >16.5%		
Caton et al. ²¹	8	Gibson and Evans	PV of series 1 month post partum = 5% of BV				4,088	63.6				
Tysoe and Lowenstein	14	Gibson and Evelyn Gibson and Evans	Average of series 1 week post partum	6,090 >34.8%	93.8 >23.9%	3,631 >31%	4,067 >44.3%	62.6 >32%	2,425 >40.4%	2,023 >19%	31.1 >9.5%	1,206 >15%

TABLE III. COMPARISON OF BLOOD VOLUME STUDIES IN PREGNANCY
TENTH LUNAR MONTH

AUTHORITY	NO. OF CASES	METHOD	NONPREGNANT STANDARD	TBV/ C.C.	TBV/ KG.	TBV/ SQ. M.	PV/ C.C.	PV/ KG.	PV/ SQ. M.	RBCV/ C.C.	RBCV/ KG.	RBCV/ SQ. M.
Thomson et al. ¹³	14	Gibson and Evans	28 TBV = 3,920 (3,110-4,870)	5,190 >32%	77.2 >7.7%		3,620 >50%	52.8		1,681		
Roscoe and Donaldson ¹⁹	20	Davis	28 TBV = 2,660 c.c./ sq. M. = 74.5 c.c./ kg.	5,400 >26%		3,180 >18%				1,950 >18%		1,160 >9%
McLennan and Thoin ³²	20	Morris	10 TBV = 3,974 PV = 2,326 RBC = 1,649	5,254 >32%			3,277 >41%			1,978 >20%		
Caton et al. ²¹	8	Gibson and Evans	PV of series 1 month post partum = 5% of BV				3,810	57.6				
Tysoe and Lowenstein	14	Gibson and Evelyn	Average of series 1 week post partum	5,784 >28%	86.8 >14.3%	3,407 >22.9%	3,802 >34%	57.1 >20.5%	2,240 >29.7%	1,982 >17%	29.7 >5%	1,166 >11%

TABLE IV. COMPARISON OF BLOOD VOLUME STUDIES
Post Partum

AUTHORITY	NO. OF CASES	METHOD	NONPREGNANT STANDARD	TIME OF BLOOD VOLUMES POST PARTUM	TIME OF RETURN TO NORMAL POST PARTUM	TBV/ C.C.	TBV/ KG.	TBV/ SQ. M.	PV/ C.C.	PV/ KG.	PV/ SQ. M.	RBCV/ C.C.	RBCV/ KG.	RBCV/ SQ. M.
Thomson et al. ¹³	14	Gibson and Evans	28 TBV = 3,920 (3,110-4,870)	2 weeks	2 weeks	3,987			2,106					
McLennan and Thoin ³²	20	Morris	10 TBV = 3,974 PV = 2,326 RBCV = 1,649	1 week	1 week	4,187 <20%			2,530 <23%			1,657 <16%		
Caton et al. ²¹	8	Gibson and Evans	PV of series 1 month post partum = 5% of BVA	1 week 1 month	1 month				3,464 2,632	50.8 50				
Tysoe and Lowenstein	14	Gibson and Evelyn Gibson and Evans	Average of series 1 week post partum	1 week 1 month 2 months	1 week	4,565 <21% 4,612	76.7 <12% 76.2	2,815 <17.3% 2,832	2,885 <24% 2,911	48.5 <15% 48.1	1,780 <20.5% 1,784	1,679 <15% 1,723	28.2 <5% 28.1	1,036 <11% 1,044
						4,517	78.7	2,831	2,772	48.3	1,737	1,745	30.3	1,092

was smaller. The higher nonpregnant normal total volumes of this series account for this discrepancy, which disappeared when the results were expressed as cubic centimeters per kilogram or square meter. The plasma volumes of this series approximated closely those found by Caton and his co-workers.

Tenth Lunar Month (Table III).—

The relatively high average of the total blood volume in the tenth lunar month would be expected from the high nonpregnant normal of this series. The percentage increases were comparable to those found by other authors. Smaller blood and plasma volumes per kilogram of body weight were found by Thomson and associates. On the other hand the results were similar to those of Rosecoe and Donaldson, when expressed as volume per square meter of surface area. As in the ninth lunar month the plasma volume approximated those of Caton. The red cell volume agreed well with that in other reports.

Post Partum (Table IV).—

It is apparent from this table that the average total blood, plasma and red cell volumes were essentially the same 1 week, 1 month, and 2 months post partum, particularly if expressed in terms of body weight or surface area. The plasma volume of this series did not change significantly from the first week to the second month. Caton and co-authors found a marked decrease between 7 and 30 days post partum, but when expressed as plasma volume per kilogram there was no significant change from the seventeenth to the thirtieth postpartum day and no significant difference in the findings of the two series.

Correlation of Hemoglobin Concentration, Red Cell Count, and Hematocrit Determination With Blood Volume Changes.—

The average hemoglobin concentration, hematocrit, and red cell counts may be discussed together because all three showed the same general trend throughout pregnancy and the same general relationship to the blood volume findings (Fig. 1).

Although the total hemoglobin mass rose from 553.4 grams in the second month to 725.5 grams in the seventh month, the changes in plasma volume were more rapid and of greater magnitude than the changes of total hemoglobin mass or of total red cell volume. Consequently, shifts of values for hematocrit, hemoglobin concentrations, and red cell count during pregnancy were largely dependent upon hydremia. Thus, from the third to the eighth month the hematocrit dropped from 38 to 34 per cent, the hemoglobin from 13.4 to 11.6 Gm. per cent and the red cell count from 4.4 to 3.8 million. Had the red cell volume and hemoglobin mass not increased, the disproportionate increase of plasma volume would have caused a greater decrease of hemoglobin concentration, red cell count, and hematocrit than was actually observed. Correspondingly, the slight decrease of plasma volume during the last antepartum month was responsible for a minimum rise of hematocrit, red cell count, and hemoglobin concentration, although the total red cell volume and total hemoglobin mass decreased slightly.

Post partum there was an initial hemoconcentration. Minimal hematologic values were obtained on the fourth day with a hematocrit of 34 per cent, red cell count of 3.75 million, hemoglobin concentration of 11.3 Gm. per cent and total hemoglobin mass of 464.8 Gm. The apparent blood loss calculated from blood volume changes was much greater than the visual estimate of the attending obstetrician and also exceeded the directly measured blood loss reported in the literature. This problem is under current study and the results will be reported subsequently.

From the eighth to the sixtieth day neither the red cell count nor the hematocrit increased significantly from their respective values of 4.19 million

BLOOD STUDIES IN PREGNANCY AND THE PUERPERIUM.

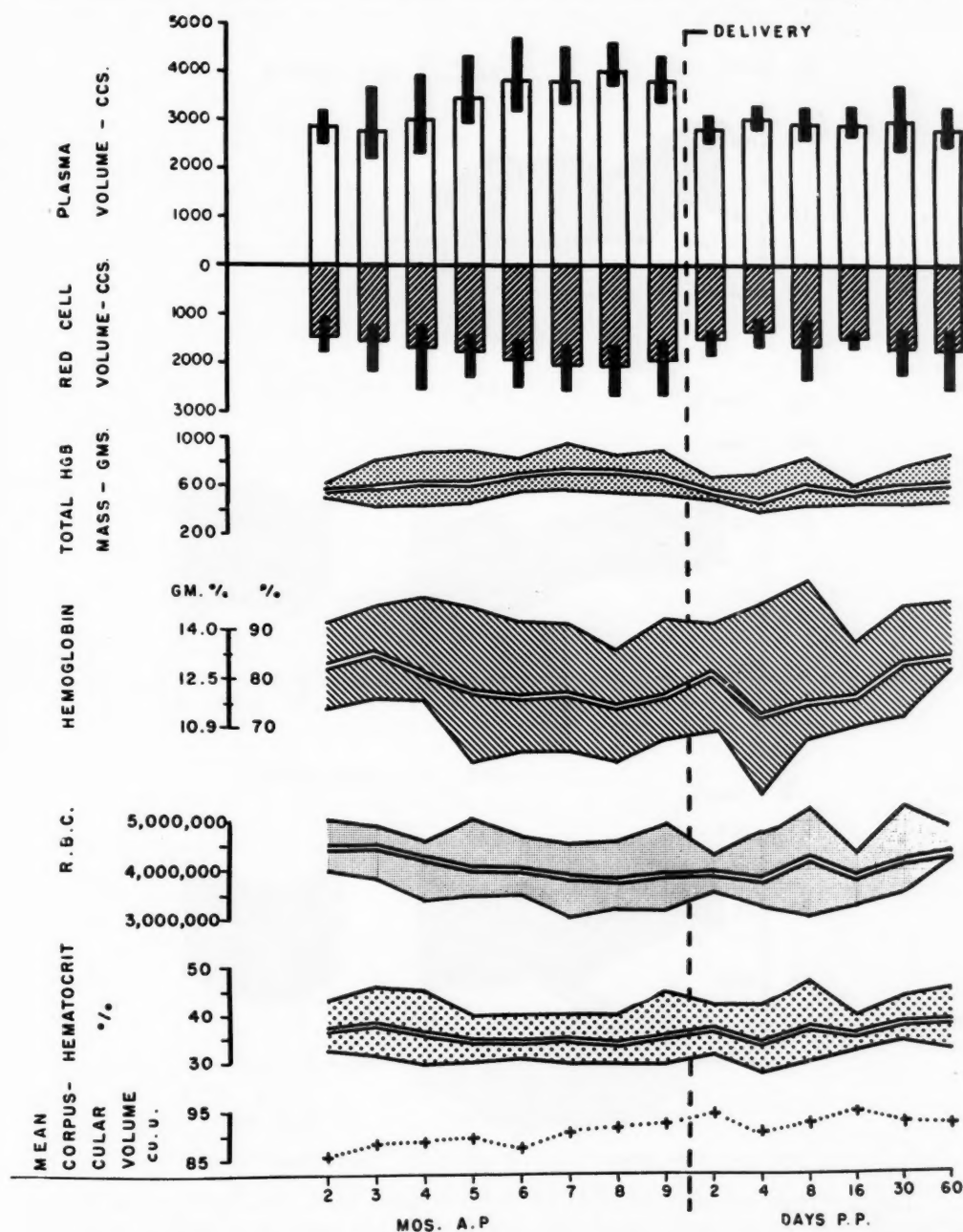


Fig. 1.—Serial blood studies of 14 normal women in pregnancy and the puerperium. Plasma and red cell volume: Large columns represent average values. Small black columns represent minimum and maximum extremes. Red cell volume, total Hgb. mass, Hgb., R.B.C., and hematocrit: Shaded areas represent minimum and maximum extremes. White lines represent the average values.

and 38 per cent. However, the hemoglobin rose less rapidly although steadily from 11.3 Gm. per cent on the fourth day to 13.2 Gm. per cent on the sixtieth day with a corresponding increase of total hemoglobin mass from 464.8 Gm. on the fourth to 604.6 Gm. on the sixtieth day.

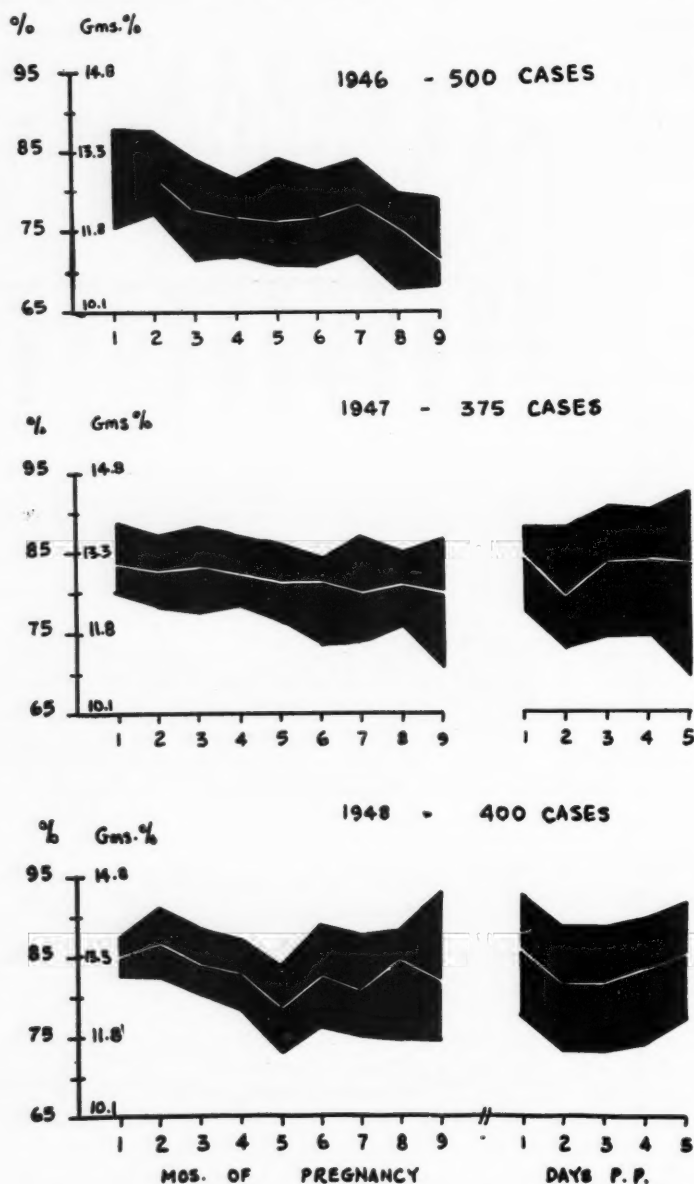


Fig. 2.—Hemoglobin in pregnancy and postpartum period.

The average mean corpuscular volume increased throughout pregnancy, although the values remained within normal limits both ante partum and postpartum. The mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration did not change significantly. Throughout pregnancy blood smears show no qualitative abnormality of the red cells.

The scatters of the blood volume, the red cell, the hemoglobin, and the hematocrit determinations varied so widely that it was impossible to predict

accurately any one of these values in a given patient at any period of pregnancy or the puerperium. The same statement applied when the blood volumes were calculated per kilogram or per square meter. When the serial values of individual cases were plotted separately the inconstancy of time and amount of change of these values in pregnancy was even more apparent.

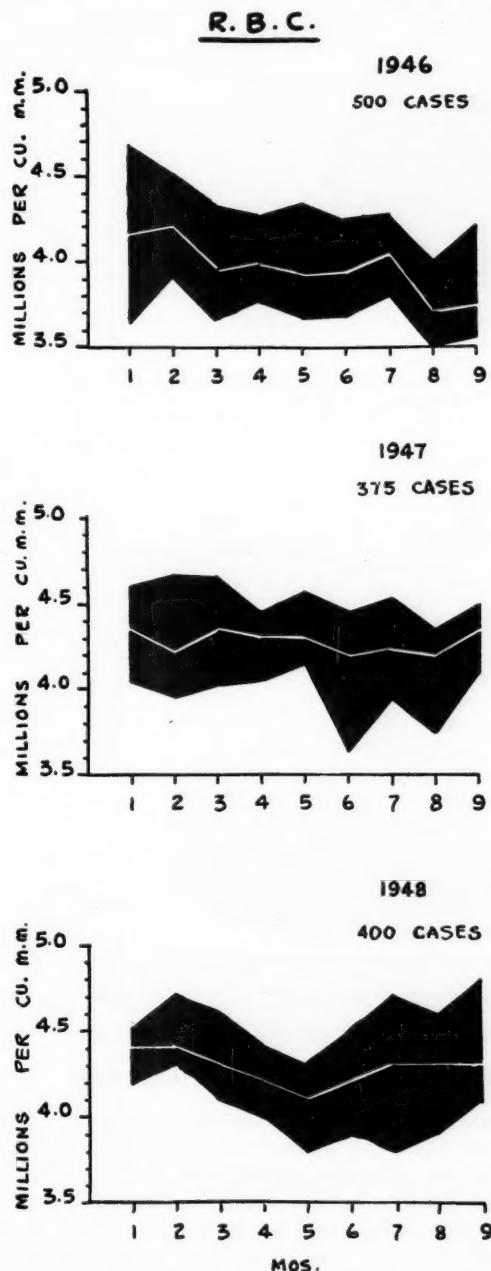


Fig. 3.—Red blood cells in pregnancy.

Both the scatters and mathematical computation showed that the individual hemoglobin concentrations and red cell counts varied more widely than the hematocrit readings at any one stage of pregnancy and the postpartum period.

Consequently, the hematocrit would seem to be the most reliable single determination of the three. It would be unwise to perform only hematocrit determinations for this procedure alone may not reflect abnormalities of the red cell. It failed to demonstrate the postpartum lag of hemoglobin synthesis of this series of patients and might well fail to reflect a mild macrocytic anemia or iron deficiency anemia.

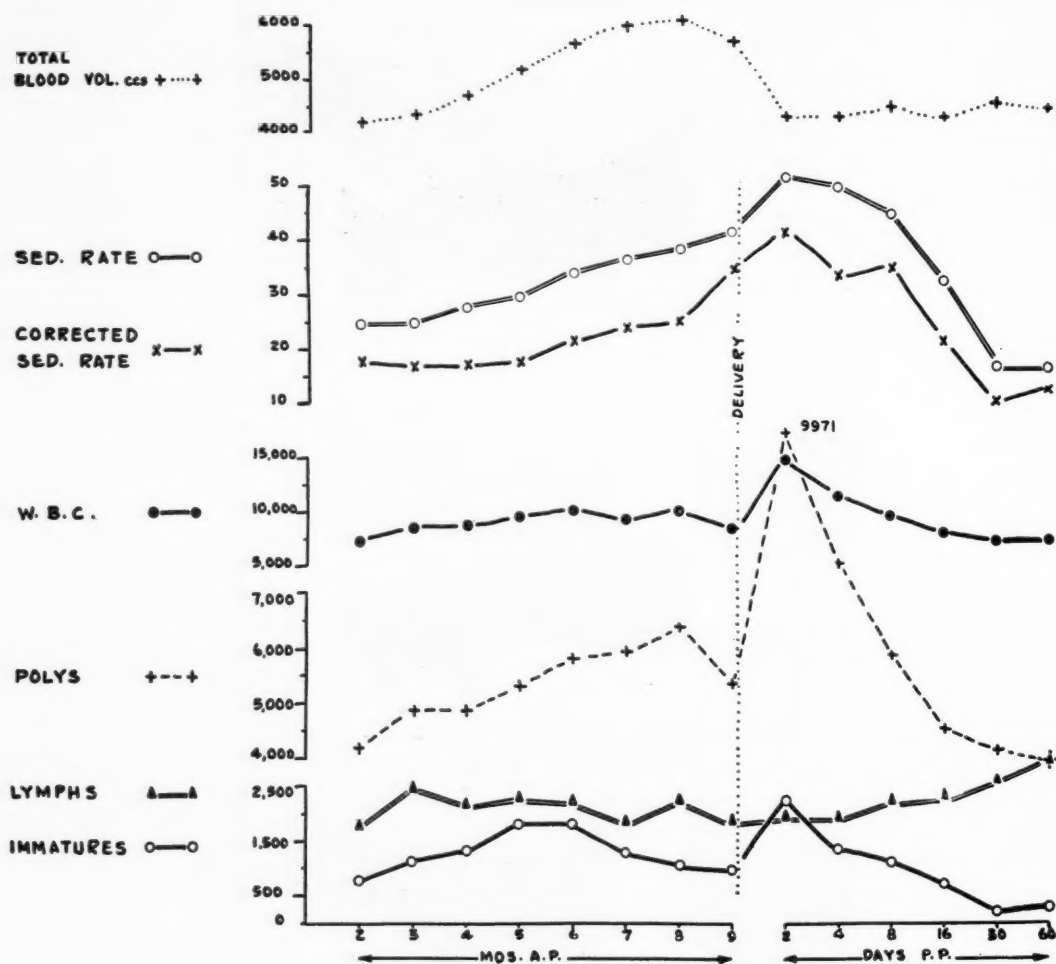


Fig. 4.—Antepartum and postpartum studies of sedimentation rate and leucocytes.

Hemoglobin and Red Cell Survey

The average hemoglobin concentrations and red cell counts of the serially studied group of patients (Fig. 1) were compared with the median and middle quartile values of the larger surveys of the years 1946, 1947, and 1948 (Figs. 2 and 3). Although the larger series exhibited some variations between the three years, certain observations may be recorded. The medians of the large series showed the same general trend as the averages of the small group. Only rarely did the minimum and maximum values of the serially studied cases lie outside the middle quartiles of the larger survey. These middle quartiles resemble the smaller group in their tendency to rise or level off with the approach of term. No consistent trend of the red cells, however, was noted in the survey series during the first trimester from year to year. Post partum,

the hemoglobin values of the survey group showed the same general trend as the serially studied patients. From this comparison it may be concluded that the values of the serially studied patients compare favorably with the middle 50 per cent values of the large groups surveyed from 1946 to 1948.

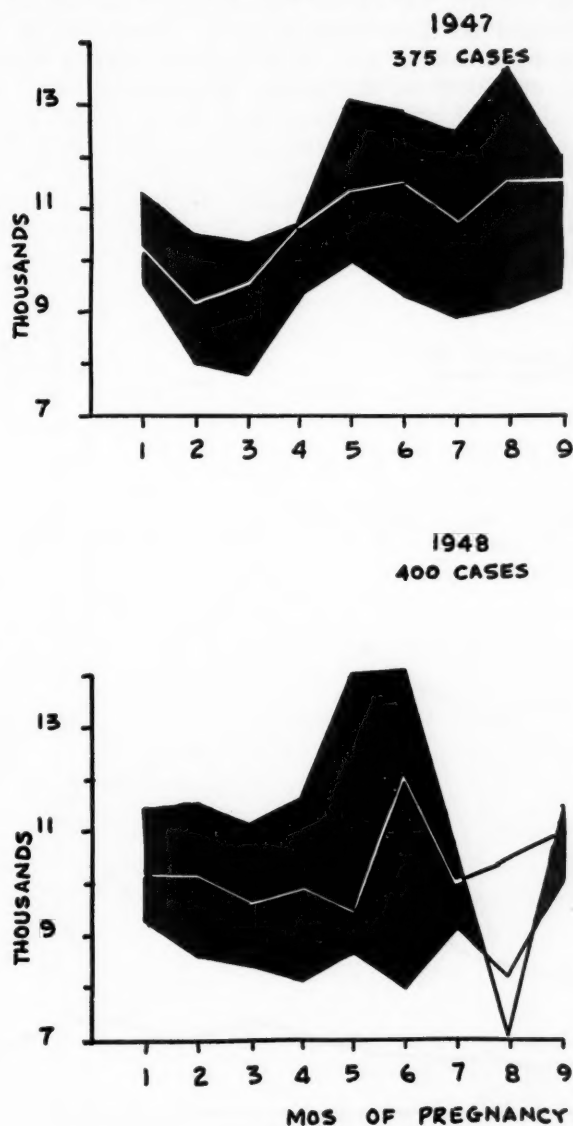


Fig. 5.—White blood cells in pregnancy.

Sedimentation Rate

The effect of hydremia on the sedimentation rate is depicted in Fig. 4. Uncorrected, the sedimentation rate rises earlier in pregnancy and is greater than when corrected by the method of Wintrobe. The corrected sedimentation rate progressively increased from the sixth antepartum month until an average of 30 mm. was obtained shortly before delivery. Post partum it fell from its peak of 37 mm. the day after delivery to within the normal range on the sixteenth day.

White Blood Cells

The average white cell count of this series increased during pregnancy (Fig. 4). The initial antepartum white cell counts averaged 7,500. After the second antepartum month, the count was higher throughout the antepartum period than at 30 and 60 days post partum. The average white cell count was 10,443 in the sixth month and 10,285 in the eighth month with a sharp rise to an average of 14,830 on the second postpartum day. A gradual recession followed until the thirtieth day, when the average white cell count of 7,451 approximated the first antepartum value. A rise of both mature and immature neutrophils caused the increase of leucocytes. As the neutrophils rose the lymphocytes reciprocally decreased during the antepartum and early postpartum periods. As the neutrophils decreased post partum the lymphocytes progressively increased.

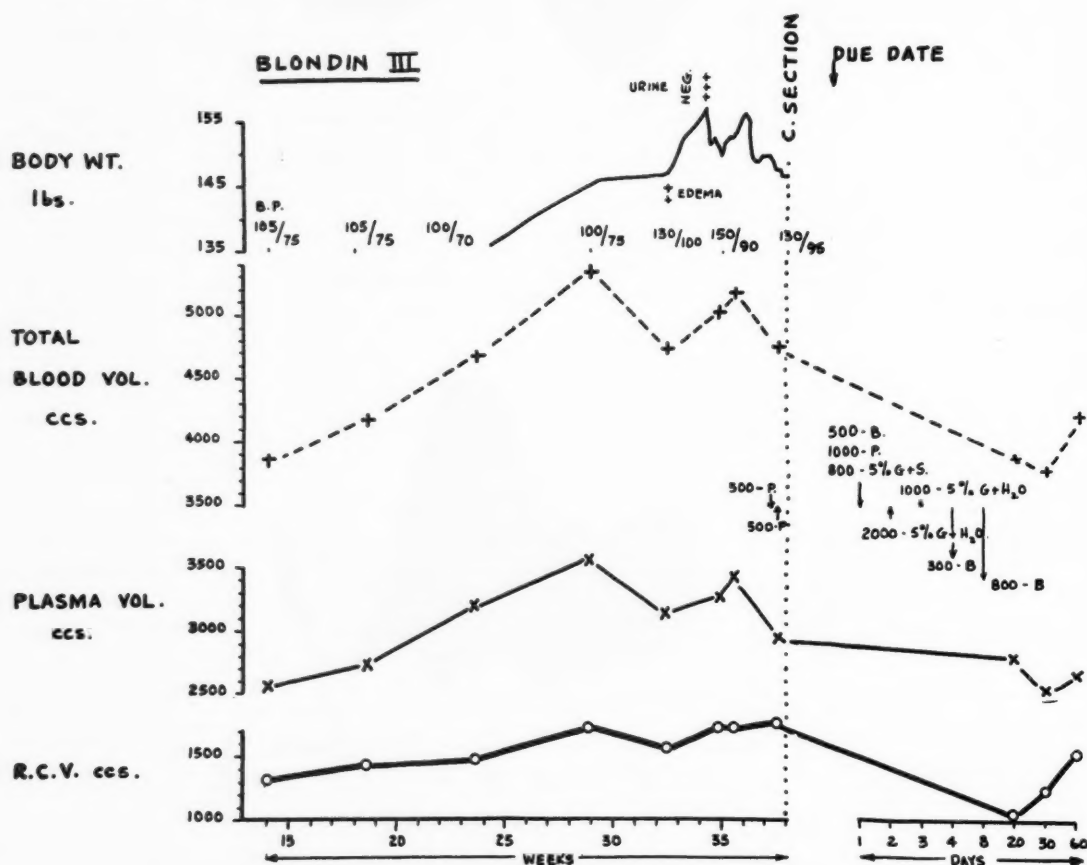


Fig. 6 (Case 1).—Pre-eclampsia. Blood volume studies.

White Blood Cell Survey

Fig. 5 represents the median and middle 50 per cent of antepartum white cell counts surveyed during the last half of 1947 and 1948. During the second and third trimesters the median of these two series was higher than the cases serially studied, reaching peaks slightly over 11,000. Marked individual variations were reflected in the wide spread of the middle quartiles.

Complicated Cases

Case 1: Pre-eclampsia Terminated by Cesarean Section (Figs. 6 and 7).—

This patient was a 24-year-old primipara who developed hypertension, edema, and albuminuria after the twenty-ninth week of pregnancy. A period of rapid gain of weight, during which the blood volume continued to rise, preceded the development of toxic symptoms. Her weight then remained stationary for 4 weeks and the total blood and plasma volumes decreased, probably due to shift of fluid to the extravascular space, as she be-

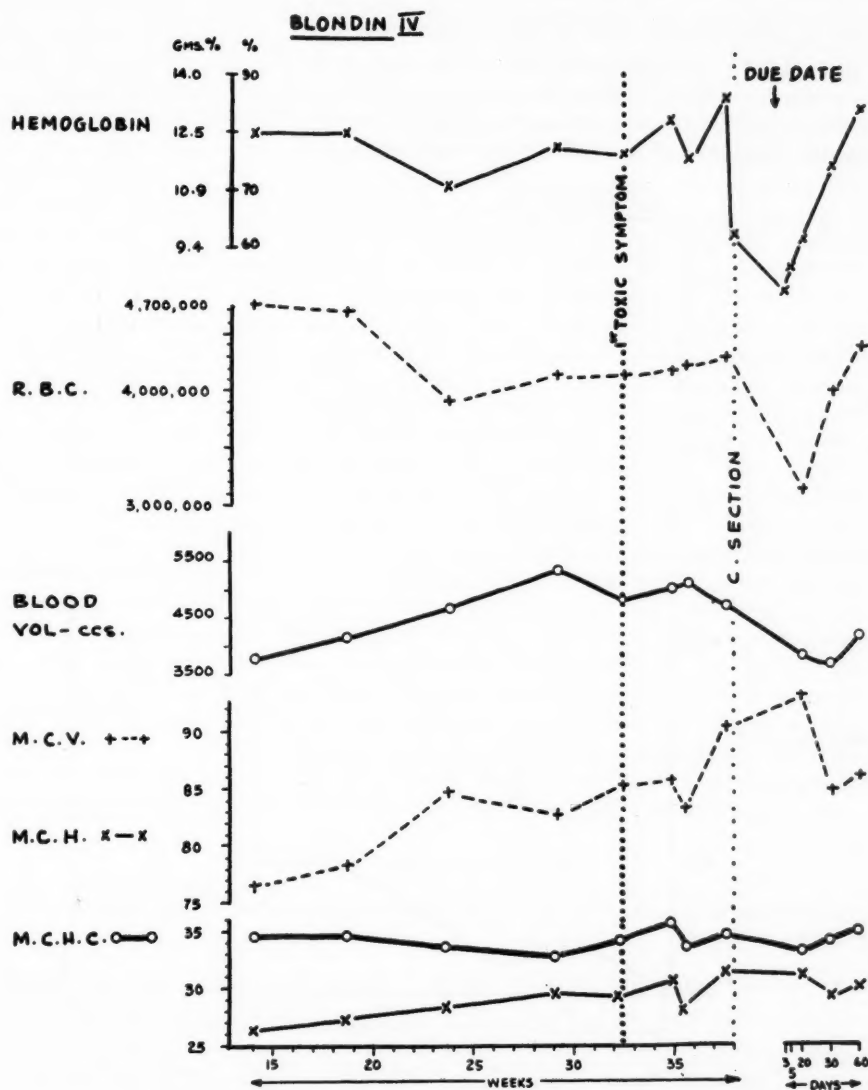


Fig. 7 (Case 1).—Pre-eclampsia. Blood volume and red cell studies.

came edematous and her blood pressure rose. Although the total red cell volume and hemoglobin mass decreased slightly during this period, the red cell count and hemoglobin concentration rose, probably due to loss of intravascular fluid. These findings are the opposite of the normal trend. It is of interest that toxic symptoms were attended by a definite lymphocytosis and reciprocal depression of neutrophils.

Post partum, her hemoglobin concentration dropped from the preoperative level of 13.4 Gm. per cent to 8.3 Gm. per cent and for 24 hours she was in shock, although transfused with 2,000 c.c. of plasma and 500 c.c. of blood. The first postpartum blood volume determination was not performed until the twentieth day due to the gravity of her condition, at which time and subsequently, changes of total hemoglobin mass paralleled changes of hemoglobin concentrations. The observed blood loss was insufficient to account for the precipitous fall of hemoglobin; it is difficult to explain this fall and the 12-day delay between the last blood transfusion and the rise of hemoglobin concentration, red cell count, total red cell volume, and hemoglobin mass.

Case 2: Placenta Previa With Cesarean Section.—

This patient's pregnancy was uneventful until slight bleeding developed in the thirty-seventh week for which cesarean section was performed in the thirty-eighth week. Blood volume and hematologic studies at well-regulated intervals ante partum and post partum did not vary significantly from those of the uncomplicated cases.

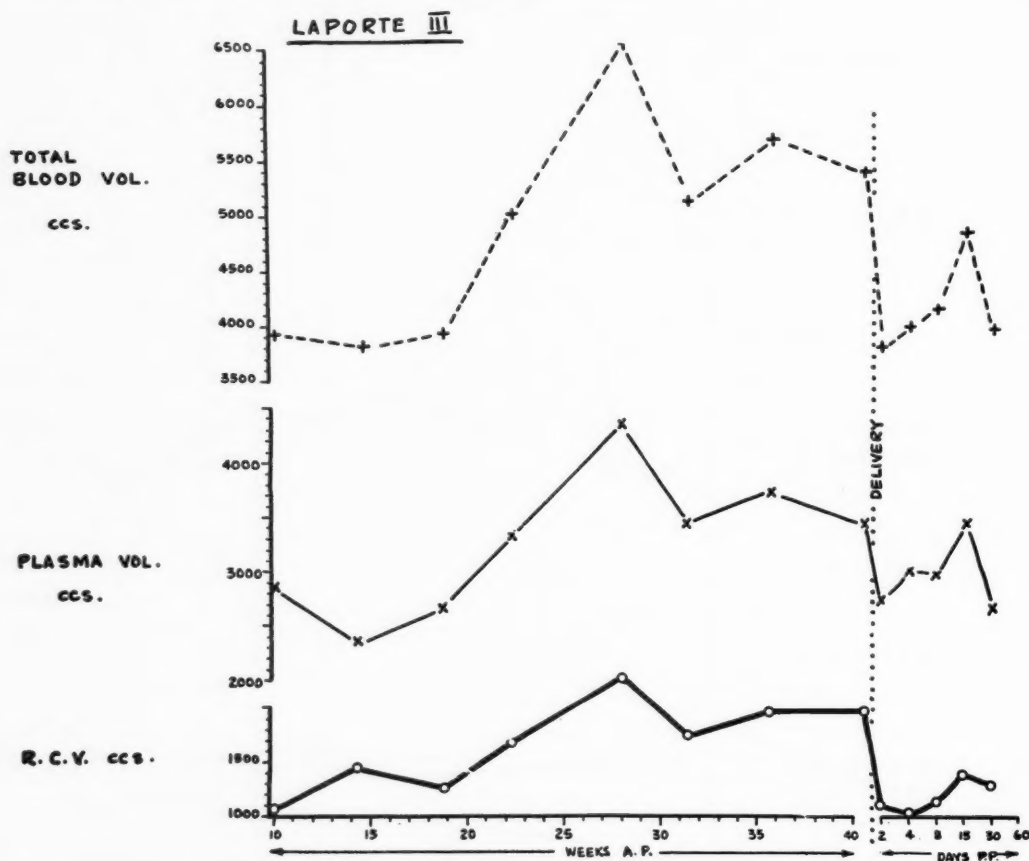


Fig. 8 (Case 3).—Postpartum hemorrhage. Blood volume studies.

Case 3: A Case of Postpartum Hemorrhage (Fig. 8).—

This patient's course was normal until she developed a postpartum hemorrhage at delivery. The last antepartum and first postpartum blood volume and hematologic studies were performed within 24 hours. Between these two observations the blood volume decreased by 1,600 c.c., the plasma volume by only 700 c.c., and the red cell volume by 900 c.c., although the total blood loss estimated at delivery and recorded on the chart was 600 c.c. As in the uncomplicated deliveries the apparent blood loss calculated from blood volume studies exceeded the estimated loss of blood.

On the day before delivery, the day after delivery, and on the fourth postpartum day, the hemoglobin concentrations were 13.1 Gm. per cent, 10.4 Gm. per cent, and 9.2 Gm. per cent, respectively, with corresponding red cell counts of 4.2, 2.99, and 2.6 millions; thus, the actual blood loss was considerable. By the sixtieth postpartum day the hemoglobin had spontaneously recovered to 14.0 Gm. per cent and the red cells to 4.3 million.

Practical Application for Routine Hematologic Studies in Pregnancy and the Puerperium

The total blood, plasma, and red cell volumes, the hemoglobin concentration, the packed cell volume, and red cell counts of this series showed certain significant changes and trends which have been discussed. Attention was focused on the impossibility of accurately predicting normal values of any of these determinations for a given patient at any stage of pregnancy or the puerperium. Moreover, it is impractical to determine the blood volume in the routine care of pregnancy. A variable hydremia may cause wide fluctuations of either the hemoglobin, the hematocrit, or the red cell values. It is well known that these values in the physiologic and pathologic anemias of pregnancy and the puerperium have a wide zone of overlap. Hence, the determination of any one of these values may not differentiate physiologic from pathologic anemias of pregnancy. How, then, may these two groups be distinguished? The key to the solution of this problem would seem to be the presence or absence of abnormalities of the red cell. Although the patients of this series exhibited marked quantitative variation of the red cell count and hemoglobin concentration, none showed significant alteration of cell size, shape, corpuscular hemoglobin content or concentration. The presence of hypochromia, microcytosis, macrocytosis, or dimorphism of the red cell would seem to indicate the probable existence of a pathologic state in this wide zone of overlap. For screening purposes the majority of such instances should be detected by routine performance simultaneously of hemoglobin concentration, red cell count, and hematocrit during pregnancy and the puerperium. Color index, volume index, mean corpuscular volume, mean corpuscular hemoglobin content, and mean corpuscular hemoglobin concentration, or other similar values may be computed from these results and the majority of instances detected in which abnormalities of the red cell exist. If abnormalities are discovered then more elaborate hematologic investigation should be undertaken, including further studies of the blood and bone marrow. The importance of including the hematocrit in these routine studies was discussed earlier.

Summary and Conclusions

1. The literature upon the hematologic and blood volume changes in pregnancy and the postpartum period was reviewed.
2. Serial hematologic and blood volume studies were performed during pregnancy and post partum in 15 women.
3. One patient of this group developed pre-eclampsia, another placenta previa, and a third postpartum hemorrhage. Their findings were discussed separately.
4. Hematologic values of this series were compared with those of 3 large groups of pregnant women studied from 1946 to 1948.
5. The blood, plasma, and red cell volumes increased during pregnancy. There was a slight decrease from the maximum values during the last 60 days, usually in the tenth lunar month. The plasma volume changes were greater than the red cell volume changes.

6. The blood volume in cubic centimeters, per kilogram or per square meter, cannot be predicted in any individual patient at any given stage of pregnancy.

7. The normal nonpregnant blood volume was attained by one week post partum and accurately represented the nonpregnant blood volume of a given patient. Our results suggest that this normal value may be reached even earlier.

8. The antepartum rise of blood volume varied in its pattern and degree from patient to patient.

9. The red cell count, hematocrit, and hemoglobin concentration fell during pregnancy. This fall was caused by and varied directly with the increase of plasma volume which exceeded the increase of total hemoglobin mass and red cell volume. No significant change of red cell count or hematocrit occurred after the eighth postpartum day, although the hemoglobin concentration continued to rise slightly to the sixtieth postpartum day.

The hemoglobin and red cell values of this serial study compared favorably with those of the middle 50 per cent of three large representative cross sections of the years 1946, 1947, and 1948.

10. The mean corpuscular volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, color index, and appearance of the red cells did not vary from the nonpregnant normal.

11. The sedimentation rate increased during pregnancy; when corrected for hemodilution this increase did not begin until the sixth calendar month. Normal nonpregnant levels were attained by 30 days post partum.

12. The leucocyte count increased progressively during pregnancy due to a rise of neutrophils. In comparison, the large individual series of 1947 and 1948 showed a slightly greater leucocytosis during the latter part of pregnancy.

Post partum, after the maximum leucocyte count was reached on the second day, the white cells gradually decreased to the thirtieth day.

13. In one case of pre-eclampsia the blood volume declined with the onset of edema and other toxic symptoms.

14. In one case of cesarean section for placenta previa the blood volume and hematologic findings corresponded to those of a normal delivery.

15. In one case of postpartum hemorrhage the decrease of blood volume was much greater than the estimated blood loss. A rapid and spontaneous recovery of the hemoglobin and red blood cells occurred post partum without antianemia therapy.

16. Routine determinations of hemoglobin concentration, red cell count, and the hematocrit are useful screening measures to detect many of the pathologic anemias of pregnancy and the puerperium.

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**CORRELATION OF BLOOD LOSS WITH BLOOD VOLUME AND OTHER
HEMATOLOGICAL STUDIES BEFORE, DURING, AND
AFTER CHILDBIRTH*†**

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POSTPARTUM hemorrhage is today a major cause of maternal morbidity and mortality.^{1, 2} Previous hematologic and blood volume studies of the normal pregnancy and puerperium at the Royal Victoria Hospital showed that the loss of circulating blood due to childbirth greatly exceeded the obstetrician's estimate. The present study was initiated to explain this discrepancy and to determine in greater detail the blood loss in normal delivery.

Many observers have measured blood loss during the third stage of labor, using receptacles to collect blood escaping from the vagina and perineum. Table I demonstrates the wide variations found in fifteen reported series.³⁻¹⁰ The average blood loss ranged from 150 to 600 ml. At the Royal Victoria Hospital the blood loss in normal delivery is commonly estimated at 200 ml. or less by the attending obstetrician. Tysoe and Lowenstein¹¹ followed the serial blood volume changes of a group of women during pregnancy and for two months post partum at the Royal Victoria Hospital and were impressed with the marked diminution of total red cell volume after delivery (Fig. 4). In recent years the T-1824 dye-hematoerit, carbon monoxide, red cell differential agglutination, and radioactive tracer methods of blood volume determination have been applied to the measurement of blood loss resulting from surgical operations, traumatic injuries, battle casualties, and gastrointestinal hemorrhage.¹²⁻²³ A number of authors have used one or more of these methods in measuring blood volumes in pregnancy and the puerperium. Table II is a composite table computed from their data.^{11, 24, 25, 26, 27} Although the number of cases reported in each series was small, their close agreement seems significant. The average apparent blood loss by these methods ranged from 810 to 1,250 ml. These findings suggested that maternal blood loss from the active circulation occurring after delivery is greater than is commonly believed and led to the following studies.

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TABLE I. BLOOD LOSS MEASURED IN NORMAL CHILDBIRTH (1919-1948)

NAME	NO. OF CASES	AVERAGE BLOOD LOSS	
		ML.	
Williams	1,000	343	
Litzenberg	3,002	462	
De Lee		500	
Ahlfeld		500	
Tarnier		600	
Plass	1,157	317	
Calkins		179	
Brandt		195	
Pastore	500	242	
Conn	800 primip	388	
			323
	1,200 multip	280	
Bickerstaff	2,015	150	
Davis	1,000	150	
Quigley	430	211	
White	300	273	
Carroll	70	301	
Range 150-600 ml.			

TABLE II. BLOOD LOSS IN NORMAL CHILDBIRTH CALCULATED FROM BLOOD VOLUME CHANGES
AVERAGE LOSS

NAME	DATE	NO. OF CASES	RED CELLS	WHOLE BLOOD	METHOD
			ML.	ML.	
Thomson, et al.	1938	15	329	1,163	T-1824 Dye
McLennan and Thouin	1948	20	283	810	T-1824 Dye
Caton, et al.	1949	10	318	947	T-1824 Dye
Tysoe and Lowenstein	1949	13	430	1,248	T-1824 Dye
Rath, Caton, et al.	1950	21	500	1,250	Radioactive Erythrocytes
Range 810-1,250 ml.					

Methods

The hematologic techniques and blood volume determinations with the dye T-1824 used in this study were those previously outlined by Tysoe and Lowenstein.¹¹

The T-1824 dye-hematocrit method has been reported to result in red cell volume values 2 to 20 per cent higher than the radioactive tracer methods.²⁸⁻³¹ This, however, does not affect the results obtained when serial determinations of the red cell volume are made with T-1824.

Plasma volume changes due to exertion and hormonal factors cause alterations of the total blood volume which do not reflect true blood loss. For this reason it was felt that blood loss should be determined by the changes of red cell volume and the formula:

$$\frac{\text{Antepartum Red Cell Volume} - \text{Postpartum Red Cell Volume} \times 100}{\text{Antepartum Hematocrit}}$$

was used to determine the apparent loss of whole blood from the circulation. Throughout this study the day of delivery is taken as the first postpartum day.

The complete findings in individual cases appear in Tables III, IV, and V.

Results

In Figs. 1, 2, and 3, which depict the results of Series A, B, and C, respectively, the case with the minimum apparent blood loss by blood volume meth-

TABLE III. BLOOD VOLUME CHANGES IN CHILDBIRTH, SERIES A (14 CASES)

CASE NO.	AGE (YR.)	GRAV-IDA	BABY'S WEIGHT (GRAMS)	FOR-CEPS	EPIS.	3RD. ST.	ANTEPARTUM				POSTPARTUM P2				POSTPARTUM D8				BLOOD LOSS		
							HCT*	HB.	BL.	RBC VOL.	HCT*	HB.	BL.	RBC VOL.	HCT*	HB.	BL.	RBC VOL.	OBST. ESTI-MATE	CALC. CELLS	(B.V.) WHOLE BLOOD
1	23	3	2,929	-	-	5	36	11.8	7022	2429	38	12.5	5360	1956	39	12.9	4723	1766	150	473	1315
2	17	1	2,551	-	-	15	39	13.6	4597	1719	38	13.7	3811	1391	39	14.3	3723	1392	250	328	840
3	36	1	3,770	-	-	4	35	12.3	5391	1811	29	10.3	4513	1254	32	11.1	4249	1304	300	557	1590
4	36	4	3,345	-	-	-	40	14.0	5641	2166	40	13.6	4465	1714	36	13.1	4348	1504	-	452	1130
5	27	2	3,144	-	-	3	39	13.6	6293	2353	35	12.0	4945	1661	35	12.0	5421	1821	200	692	1775
6	24	1	3,628	-	-	5	43	15.1	5763	2380	40	14.3	5047	1938	37	13.1	5497	1951	250	442	1025
7	21	1	3,404	-	-	27	40	13.6	6530	2507	39	12.9	5827	2179	39	12.8	5332	1994	300	328	820
8	29	2	3,259	-	-	3	37	12.8	5308	1884	37	12.8	4765	1691	38	12.9	4601	1679	200	193	522
9	28	5	3,827	-	-	7	31	9.1	6787	2022	30	8.9	5672	1633	33	10.1	4837	1535	150	389	1255
10	24	4	2,948	-	-	18	38	13.3	4315	1575	38	13.4	4070	1467	37	13.6	3440	1271	150	108	284
11	22	2	3,440	-	-	18	38	14.8	5946	2170	42	16.5	4797	1933	42	16.1	5003	2016	200	237	623
12	22	1	3,171	-	-	8	43	15.0	5614	2318	39	13.6	4376	1636	40	14.2	4323	1660	300	782	1820
13	26	3	3,515	-	-	1	39	13.3	5121	1915	40	13.6	3960	1464	39	13.4	4060	1509	400	451	1151
14	29	2	3,120	-	-	4	40	13.6	5806	2229	42	14.0	5244	2113	42	13.6	4616	1860	125	116	290
Average	26	2	3,290	2/7	5/7	8	38	13.2	5723	2105	37	13.0	4775	1716	37	13.0	4583	1661	214	396	1031

*Hematocrit.

TABLE IV. BLOOD VOLUME CHANGES IN CHILDBIRTH, SERIES B (14 CASES)

CASE NO.	AGE (YR.)	GRAV-IDA	BABY'S WEIGHT (GRAMS)	FOR-CEPS	EPIS.	3RD. ST.	ANTEPARTUM				POSTPARTUM D3				POSTPARTUM D8				BLOOD LOSS		
							HCT*	HB.	BL.	RBC VOL.	HCT*	HB.	BL.	RBC VOL.	HCT*	HB.	BL.	RBC VOL.	OBST. ESTI-MATE	CALC. CELLS	(B.V.) WHOLE BLOOD
1	25	1	3,540	-	-	12	39	13.6	4231	1582	31	10.0	3830	1141	38	12.6	3533	1289	300	441	1131
2	26	4	3,860	-	-	5	38	12.5	4370	1595	39	12.3	3546	1326	40	13.6	3519	1418	150	269	708
3	19	1	2,920	-	-	5	38	13.4	5568	2032	38	13.6	4245	1549	40	13.6	4133	1587	600	483	1271
4	25	5	3,404	-	-	2	35	12.5	6301	2117	39	12.8	4611	1724	39	12.5	4653	1740	250	393	1120
5	21	1	2,750	-	-	13	42	14.5	4529	1825	41	13.7	3765	1483	46	14.8	3663	1619	400	342	814
6	41	2	2,845	-	-	5	38	13.1	5236	1911	37	12.6	4370	1551	39	12.5	4166	1558	300	360	947
7	22	1	2,970	-	-	5	36	12.6	4246	1469	38	12.3	3530	1288	39	13.9	3560	1330	300	181	504
8	28	3	3,300	-	-	5	36	12.5	5882	2035	39	12.6	4952	1852	40	13.6	4922	1890	300	183	509
9	18	1	3,170	-	-	9	42	14.0	5249	2115	36	12.0	3512	1215	39	13.1	3646	1363	350	900	2140
10	20	3	3,230	-	-	8	37	12.5	4993	1772	40	13.6	4383	1683	44	14.5	4584	1934	200	89	240
11	20	3	2,945	-	-	5	40	13.4	4349	1670	27	8.6	4217	1092	38	13.3	3629	1324	450	578	1125
12	34	7	3,650	-	-	15	42	14.0	6038	2433	42	13.6	5286	2130	43	14.3	5495	2269	250	303	721
13	23	3	3,950	-	-	12	32	10.1	5959	1829	36	11.5	5022	1737	36	11.7	5006	1732	150	92	287
14	22	1	3,375	-	-	3	43	14.3	4282	1768	33	11.7	4060	1287	34	11.1	3646	1188	450	481	1118
Average	24	2	3,280	3/7	9/14	7	38	13.0	5088	1868	36	12.2	4234	1504	39	13.2	4146	1588	317	363	902

*Hematocrit.

ods is shown on the left. The case with the maximum blood loss is shown on the right and the average blood loss of the series by blood volume methods is shown in the center.

Series A (Fig. 1).—Fourteen unselected deliveries are included in this series.

BLOOD VOLUME CHANGES IN NORMAL CHILDBIRTH - SERIES A (14 CASES)

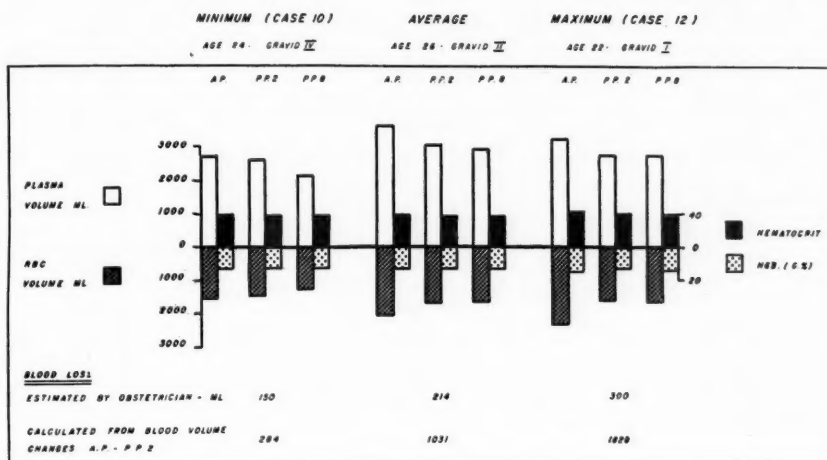


Fig. 1.

BLOOD VOLUME CHANGES IN NORMAL CHILDBIRTH - SERIES B (14 CASES)

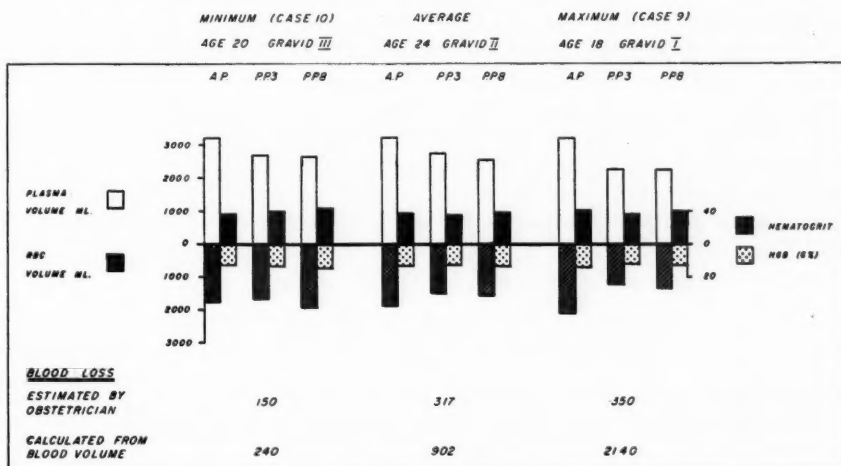


Fig. 2.

The patients were studied shortly before delivery, and on the second and eighth postpartum days. The hemoglobin concentration and hematocrit do not reflect the actual changes of plasma and red cell volumes. The apparent blood loss in Series A varied from 284 ml. to 1,820 ml., with an average of 1,031 ml. There was no significant change of red cell volume from the second to the eighth postpartum days. The blood loss estimated by the attending obstetrician was 150 to 300 ml. with an average of 214 ml.

TABLE V. BLOOD VOLUME CHANGES IN CHILDBIRTH COMPARED WITH

CASE NO.	AGE (YR.)	GRAV. IDA	BABY'S WEIGHT (GRAMS)	FOR-CEPS	EPIS.	3RD ST.	ANTEPARTUM				POSTPARTUM			
							HCT*	HB.	BL. VOL.	RBC VOL.	HCT*	HB.	BL. VOL.	RBC VOL.
1	37	4	3,620			3	4h AP 35	11.5	5817	1954	15' PP 38	11.8	4393	1603
2	31	4	3,075	-	-	6	20' AP 39	12.6	4615	1726	1h 30' PP 37	11.7	3798	1348
3	35	2	3,730	-		5	1h 30' AP 41	12.5	5295	2084	30' PP 42	13.6	4854	1956
4	30	8	3,350	-	-	5	10h AP 37	12.0	5272	1871	50' PP 42	14.0	4249	1705
5	21	2	3,940	-		5	3h AP 36	11.8	5143	1779	40' PP 37	11.8	3409	1210
6	20	2	3,360	-		7	1h 30' AP 38	12.5	6343	2315	18' PP 42	14.0	5762	2322
7	19	3	4,120	-	-	2	5h AP 40	13.3	4670	1793	31' PP 41	13.6	4174	1644
8	24	2	3,830	-	-	5	3h AP 39	12.8	4490	1679	15' PP 40	13.3	4400	1690
9	42	8	3,320	-	-	4	3h AP 38	11.4	5149	1879	18' PP 40	13.1	3912	1502
Average							38	12.2	5199	1897	39	12.9	4327	1664

*Hematocrit.

Series B (Fig. 2).—Studies identical to those of Series A were made in a group of 14 unselected deliveries except that the first studies after delivery were made on the third postpartum day in an effort to determine the day at which the red cell volume was lowest. The apparent blood loss ranged from 240 to 2,140 ml. with an average of 902 ml. The hemoglobin concentration and hematocrit did not reflect the changes which occurred in plasma and red cell volume. By the time that this series was initiated, many of the obstetricians were familiar with the results of Series A, which may account for the increase of the visually estimated blood loss. There was no significant difference between the red cell volumes on the third and eighth postpartum days.

Because of the discrepancy between blood loss estimated visually and by blood volume determinations, it was decided to measure the blood escaping from the vagina and perineum using an apparatus of the type described by Carroll.⁹ The blood collected in this apparatus was hemolyzed with water and the amount of blood was determined by the formula:

$$\frac{\text{Volume of Fluid} \times \text{Hemoglobin of Fluid}}{\text{Antepartum Hemoglobin of Patient}}$$

The patients' pads were collected for 36 to 48 hours, the lochia contained in them was hemolyzed, and their blood content was determined by the same formula.^{23, 32}

Series C (Fig. 3).—The antepartum blood volumes were determined as close to delivery as possible in these 9 patients. Postpartum studies were performed from 15 to 90 minutes after delivery and on the third and eighth postpartum days.

Multiparas were selected for this series in order to reduce the use of forceps and episiotomies and in order to avoid tears. The measured blood loss may be compared with the apparent blood loss as determined from blood volume changes. The measured blood loss at delivery ranged from 100 ml. to 485 ml. with an average of 224 ml. This may be compared with the apparent blood loss calculated from blood volume determinations immediately before

MEASUREMENT OF BLOOD LOSS. SERIES C (9 CASES) ALL MULTIPARA.

POSTPARTUM D 3				POSTPARTUM D 8				BLOOD LOSS MEASURED			CALCULATED (B.V.)			
HCT*	HB.	BL. VOL.	RBC VOL.	HCT*	HB.	BL. VOL.	RBC VOL.	AT DEL.	LOCHIA	TOTAL	RED CELLS		WHOLE BLOOD	
											AP-PP1	AP-PP3	AP-PP1	AP-PP3
34	11.4	4545	1481	37	11.7	3998	1419	116	61	177	351	473	1002	1350
29	10.1	4747	1319	33	11.4	4156	1317	448	145	593	378	409	970	1095
39	12.8	4458	1667	-	-	-	-	166	67	233	128	417	312	1018
45	15.1	3825	1652	47	15.6	3500	1578	100	68	168	166	219	448	592
31	10.6	3626	1080	29	9.5	4055	1127	485	44	529	569	699	1580	1940
43	14.5	4739	1957	-	-	-	-	270	94	364	nil	358	nil	942
37	12.5	3674	1304	40	13.6	3478	1335	230	43	273	149	489	371	1221
				42	14.0	3810	1493	106	185	291	nil	186	nil	477
36	11.2	4573	1582	39	12.6	4138	1547	100	33	133	377	297	992	781
36	12.2	4273	1505	38	12.6	3876	1402	224	82	306	235	394	630	1041

and after delivery (AP - PPI) which ranged from 448 ml. to 1,580 ml. with an average of 630 ml. The apparent blood loss increased still further when the differences between the blood volumes ante partum and on the third postpartum day were computed (AP - PP3) as was done in the Series A and B. These values ranged from 592 ml. to 1,940 ml., with an average of 1,041 ml. The amounts of blood lost as lochia during the first thirty-six to forty-eight hours post partum were relatively small, ranging from 33 to 185 ml., with an average of 82 ml.

These small amounts fail to explain the great decrease of red cell volume which occurred during the thirty-six to forty-eight hours after delivery. The measured blood loss from the vagina approximates the results of other authors and also the visually estimated blood loss of Series A and B. The apparent blood loss calculated from blood volume determinations also compares favorably with the results of other workers computed in Table II, but is much greater than the measured blood loss. The difference between the red cell volumes immediately after delivery and 36 to 48 hours later may offer the key to this discrepancy. In several individual cases this decrease was considerable, amounting in one patient to 358 ml. of red cells or 942 ml. computed as whole blood. The clinical and other hematologic observations did not indicate that this decrease was due to hemolysis as suggested by Rath, Caton, and Reid (1950). A number of authors³³⁻³⁶ have shown that blood reservoirs do not exist in man as in certain animals.

Wilson,²³ in performing similar studies with the T-1824 dye-hematocrit method on surgical cases immediately before and after operation, noted that when blood losses were large, there was marked discrepancy between measured loss and blood volume loss. He felt that this could be due to withdrawal of blood from the circulation by stagnation. He felt that anoxia and the danger to life from this phenomenon would then be disproportionate to the measured blood loss. Following delivery of the patients studied in Series A, B, and C, a similar and permanent withdrawal of red cells from the active circulation seems to have occurred. It is possible that a considerable part of these red

cells passes into the body of the uterus following delivery. This problem is under current study.

To date it has been impossible to measure directly the amount of blood contained in a uterus removed two days post partum. Three Porro cesarean sections provided contracted uteri, which were perfused and which contained, respectively, 127, 95, and 80 ml. of blood.

BLOOD VOLUME CHANGES IN NORMAL CHILDBIRTH. SERIES C (9 CASES) ALL MULTIPARA.

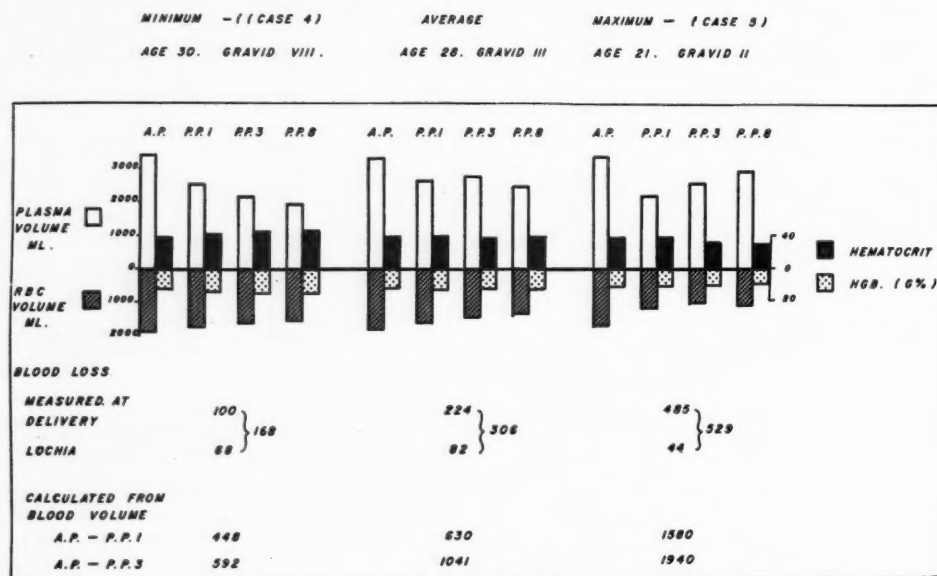


Fig. 3.

Summary and Conclusions

1. Serial hematologic and blood volume determinations using the T-1824 dye-hematocrit method were performed upon 37 patients before, and at varying intervals after delivery. In the last group of 9 patients, vaginal and perineal blood loss was measured. The red cell volumes showed no significant differences 24 hours, 48 hours, and 8 days post partum.

2. The blood volume changes in all series studied were not attended by comparable changes of the hemoglobin concentration and the hematocrit.

3. The blood loss from the active circulation in 37 normal women calculated from antepartum and postpartum blood volume changes averaged 991 ml. This greatly exceeded both the visually estimated blood loss and the directly measured blood loss.

4. It is suggested that permanent loss of blood from the active circulation accounts for this discrepancy. This loss and the increase of apparent blood loss as determined by blood volume studies 15 to 90 minutes after delivery and on the second postpartum day may be partly due to trapping of circulating blood in the body of the uterus.

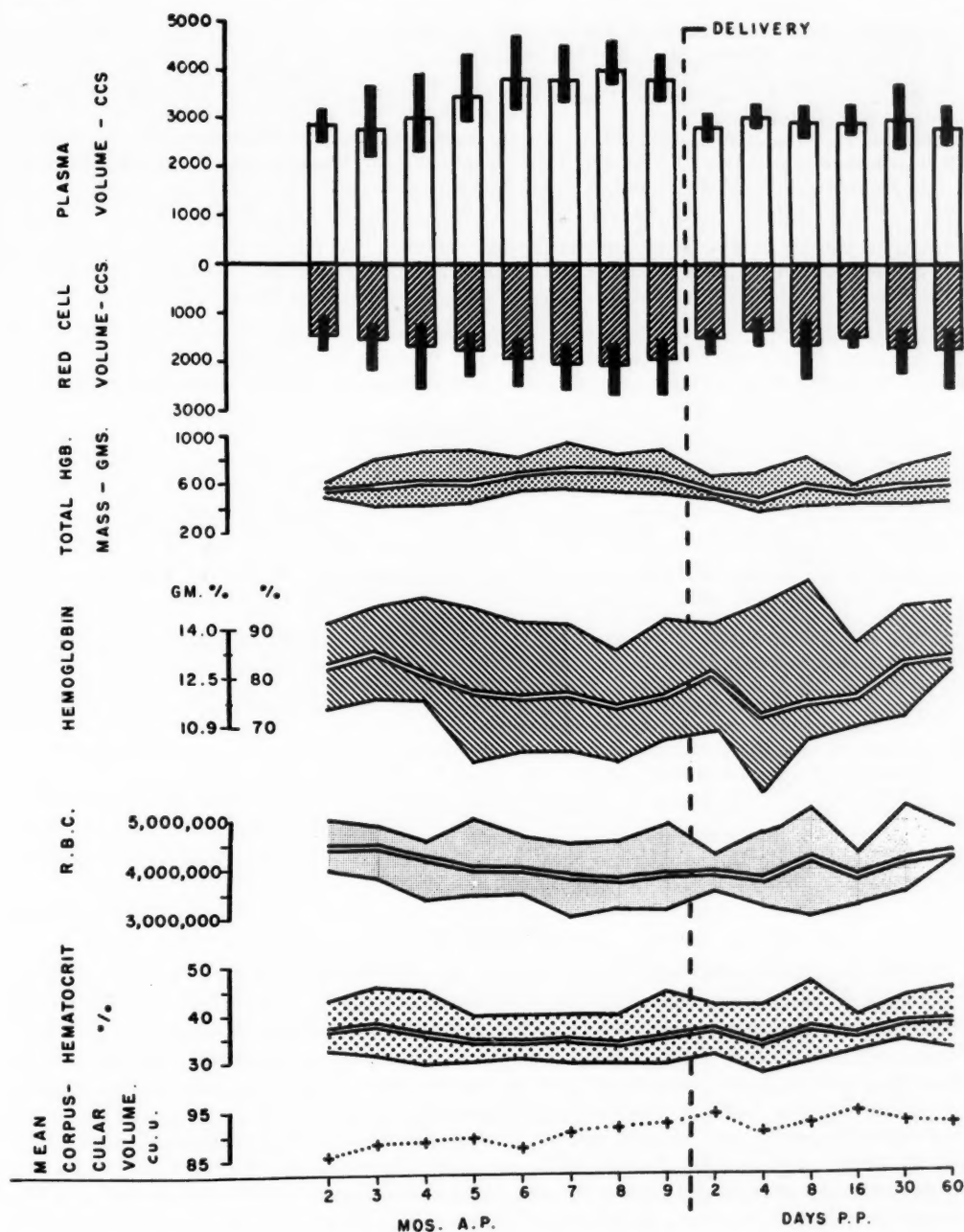


Fig. 4.—Serial hematologic and blood volume studies in 13 women during pregnancy and the postpartum period.

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Discussion

DR. H. CLOSE HESSELTINE, Chicago, Ill.—It is the ubiquitous desire of all obstetricians to prevent as much blood loss at delivery as possible. Inasmuch as Dr. Philpott's paper deals with comparative values of blood and blood fraction volumes in pregnancy, labor, and puerperium, rather than clinical methods for the prevention of blood loss, my discussion will be in the same tenor. As he has indicated, there have been a large number of studies dealing with the ranges and averages of blood loss in all types of delivery and in relation to parity, age, type of delivery, and analgesia and anesthesia, and other factors. Dr. Philpott is commended for his effort to unravel some of the discrepancies in the behavior of blood volume determination and blood loss estimates. It is hoped that the discrepancies which have been pointed out will in time be cleared.

Several reports from the Department of Obstetrics and Gynecology at the Chicago Lying-in Hospital have appeared in fairly recent years. Dieckmann and others of the department have been especially interested in the hematologic aspects. Dr. Philpott refers to Dieckmann and Daily's observations that blood loss was directly related to type of delivery; about 500 c.c. was the average blood loss with cesarean section. Dieckmann and his associates revealed the variability of human error in estimates of blood loss. There was considerable variation in the error in the estimates of measured blood. The larger the volume the greater the error, even to the degree of seriousness in clinical application. Perhaps the doctor's unconscious desire for good results may color his estimates, yet the inaccuracy of gross estimates persists.

Perhaps Oberst and Plass had a partial explanation for these changes of the blood picture as a result of fluid dilution. One approach to this over-all problem was tried by Dieckmann and Odell. Twelve patients with measured blood loss at delivery of less than 300 c.c. were treated by removal of 500 c.c. of venous blood within an hour or sooner after delivery. It was noted that by the tenth day post partum the cell volume, hemoglobin, serum protein, and albumin had as an average returned almost to the antepartum level. The immediate reaction of the host is indicated by the prompt shift and gradual recovery. It is also possible that the agents used in Dr. Philpott's test may be absorbed by certain structures—organs, cells, or fluids—or taken out of circulation in such a manner that the contradictions arise between the measured blood loss and vascular trunk determinations.

One might ask what physiologic principle could be served if a large amount of blood did enter the postpartum uterus, as has been suggested. If this should be true, then the next question is, what happens to the blood as the uterus involutes?

An attempt to determine hemoglobin loss in the lochia after the first day or so may be inaccurate because such bacteria as beta hemolytic streptococcus and *Clostridium welchii* destroy the red cells and hemoglobin, thus producing a false value.

This presentation does not give a complete answer but its straightforward description of the discrepancies presents challenges for which an answer is sought. I compliment Dr. Philpott for this description of these findings. He has given to us as scientists—especially those of us particularly interested in hemoglobin level, cell volume, water content, and protein fractions of the vascular system of the woman while pregnant, in labor, or in the puerperium—a challenge and open invitation for an answer.

DR. CARL BACHMAN, Philadelphia, Pa.—If I understand Dr. Philpott's presentation correctly, he has indicated that, regardless of how much external bleeding there may be immediately post partum, there is a constant deficit of about 500 and 800 c.c. as between the amount measured directly and the amount determined from the coincidental fall in circulating red cell volume. This means that a fairly large and constant amount of blood disappears from the circulation of every woman shortly after delivery at term. Moreover, the blood that so mysteriously disappears is apparently not available as reserve or depot blood if external hemorrhage is severe. If this be true, the phenomenon is a most interesting physiological one.

Two questions naturally arise: First, are methods of blood volume determination accurate enough to give one confidence in what has apparently been demonstrated? Second, where does the blood in question go? Dr. Philpott has found that the excised uterus in cases of Porro cesarean section does not hold enough blood to be seriously considered as the suspected reservoir. I did not, however, hear him say what the postoperative blood volume changes were in these cases of Porro cesarean section.

DR. LOUIS LOWENSTEIN, Montreal, Quebec.—Although the T-1824 dye-hematocrit method of blood volume determination ultimately will probably be replaced by more accurate methods, it has been shown to approximate the accuracy of other methods available today. In these studies serial determinations were performed by one doctor and by one technician. The serial determinations used for comparative purposes are believed to minimize the significance of increase of total red cell volume, obtained with the T-1824 dye-hematocrit method, as compared with one of the radioactive tracer methods or with the Ashby agglutination method.

These studies clearly show that the blood loss as determined by blood volume studies was three to four times greater than the measured amount of blood loss from the vagina and perineum. It is impossible at present to state finally whether this difference is due to trapping of blood in the uterus or elsewhere, although the former would seem most likely. Dr. Philpott mentioned that the uteri obtained from the Porro cesarean sections were contracted and consequently the amount of blood perfused from these uteri was small, as compared with the amount one might expect from blood volume studies. Unfortunately the contracted state of the uteri negates the value of these measurements for purposes of comparison.

These findings would seem to be of practical significance. The demands of the fetus, the increased oxidation of tissues, the increased cardiac output and circulation time and other circulatory changes, which suggest an analogy with an arteriovenous aneurysm, are adequate reasons for the increase of blood volume during pregnancy. After delivery physiologic changes require a return of the blood volume to normal nonpregnant values. This would seem to be accomplished with a minimum blood loss from the body and with conservation and reutilization of the major portion of blood lost from the active circulation. These changes would then seem to be physiologic and part of the normal body economy. Postpartum hemorrhage is believed to be the most prevalent cause of postpartum morbidity and mortality. In patients who have postpartum hemorrhage, pre-existing anemia, severe infection, or other serious diseases, removal of these amounts of blood from the active circulation may be an important contributing cause to shock or to the exaggeration of an already existing anemia.

At the Royal Victoria Hospital, hemoglobin, red cell, and hematocrit determinations are performed at intervals on all pregnant and postpartum women. This screening process has proved most helpful in the detection of anemia in pregnancy and the puerperium.

DR. PHILPOTT (Closing).—In answer to Dr. Bachman I would say that the big problem is the ninety minutes to twenty-four hours post partum, when there is a drop of 900 c.c. of whole blood volume in most cases. That is so elusive and we would like to know where it goes during that time when there is no evidence of external blood loss. Animals do not lend themselves to this study because there is a species difference. Otherwise we would, of course, be working on that.

SICKLE-CELL DISEASE AND PREGNANCY*

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SICKLE-CELL disease¹ is a hereditary, variable malady confined with few exceptions to Negroes, characterized by sickle-shaped erythrocytes, a normochromic normocytic anemia, jaundice, and thrombotic phenomena. In this paper we shall use S.C.D. to indicate sickle-cell disease or sickle-cell anemia. S.C.T. will signify sickle-cell trait or sicklemia, a condition of the blood characterized by sickling of the erythrocytes.

Diggs, Ahmann, and Bibb¹ found the incidence of S.C.T. in a study of 8,453 Negroes of various ages and both sexes to be 7.3 per cent. They reported that the ratio of S.C.D. to S.C.T. is about 1 in 40. Lewis² summarized many reports from different areas in the United States and found the average incidence of S.C.T. to be 7.48 per cent. He stated that of the persons showing S.C.T., 2.5 per cent will show S.C.D. However, Switzer and Fouché³ found an incidence of 14.2 per cent in an analysis of 500 obstetric patients in South Carolina. In our study of 1,200 consecutive Negro obstetric patients we have found an incidence of 8.3 per cent, and we believe that the S.C.D.-S.C.T. ratio in obstetric patients in New Orleans is approximately 1:138. In the absence of anemia, S.C.T. is of little clinical significance for the reasons set forth by Diggs, Ahmann, and Bibb¹; viz., it is compatible with long life, the hospital incidence is no greater than in healthy patients, hemoglobin determinations of Negro school children show parallel findings in those with and those without the trait, and the importance of S.C.T. appears to be limited to the relatively small group who have S.C.D. in addition to the trait. Switzer and Fouché³ state that of 22 sicklemic patients admitted to the Roper Hospital because of obstetric complications none exhibited evidence of S.C.D. Our experience causes us to believe that S.C.T. obstetric patients are no more prone to complications than are average Negroes; however, S.C.D. patients are very susceptible to complicating disorders.

S.C.D. has *latent* and *active* phases. The former may be prior to the active phase, being referred to as the initial stage, which dates from birth until active manifestations appear; or it may occur after the period of clinical activity, being characterized by sickling and, in most instances, anemia. In the active phase clinical symptoms of the disease become apparent. These may be mild and continue for years, being designated as chronic. The acute active phase is the stage of "crisis" and therein occurs a very striking change in manifestations consisting of pain, tachycardia, polypnea, pallor, jaundice, and fever. Death may become imminent. Although the cause of the crises is not actually known,

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For lack of space it was necessary to condense the original manuscript, references, and discussion.

it has been suggested that these dramatic attacks are due to some blood vascular phenomenon, an autonomic nervous system disturbance, infarctive or hemorrhagic episodes occurring in the spleen, obstruction of vessels supplying the central nervous system, and to an allergic state.

Incidence.—Fig. 1 shows the incidence of S.C.D. associated with pregnancy at the New Orleans Charity Hospital. From Jan. 1, 1939, to April 1, 1950, there have been 37 such pregnancies in 24 patients. In the same period there were 60,432 Negro deliveries at this institution. During the past 4 years over 80 per cent of the Negro births in New Orleans occurred in this hospital; consequently, we believe that 6 per 10,000 probably approaches the true incidence of the condition in this area, realizing that mild chronic or latent phase cases may have been undiagnosed.

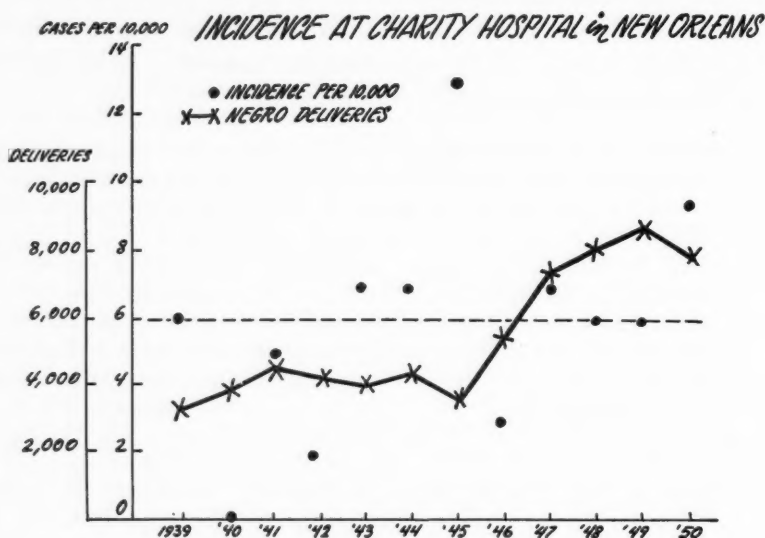


Fig. 1.

Age.—Eleven patients were in the 16 to 20 year group and 7 were in the 21 to 25 year classification. These figures are to be compared with the 24 cases in the former group and 15 in the latter as reported in the literature. Only four patients above 30 years of age were found in the reported series. One such patient, 32 years of age, appears in the Charity Hospital group. The paucity of patients above 30 years of age lies in the fact that persons with S.C.D. are likely to expire before reaching the fourth decade of life.

Gravidity.—Fifteen of the 24 patients in the Charity Hospital series have been gravid more than once. Fig. 2 reveals that 28 patients in the previously reported cases in which the gravidity was stated had only one gestation. All Charity Hospital primigravidas were under 20 years. Nine of the 14 patients with pregnancies terminating at Charity Hospital prior to January, 1949, who have survived and were not surgically sterilized, have conceived again. These data are compatible with the impression that patients having S.C.D. have fewer pregnancies than their nonafflicted sisters; nevertheless, they show that the likelihood of future conception must be considered.

Parity.—Fig. 3 indicates that a minority of the patients are multiparas and substantiates the belief that these patients have difficulty in carrying their gestations to the stage of viability. Two of the Charity Hospital group and five of those in the literature had more than one abortion.

Diagnosis

Past History.—In the Charity Hospital cases the following were found to be the outstanding past history data suggestive of S.C.D.: recurrent severe abdominal pain, jaundice, leg ulcers, joint pains, anemia, "rheumatic fever" diagnosis, recurrent respiratory infections, and pronounced malaise. One patient gave a history of splenomegaly as a child and another was feeble-minded. Having elicited any of these symptoms the investigator will be stimulated to confirm or eliminate the likelihood of S.C.D.

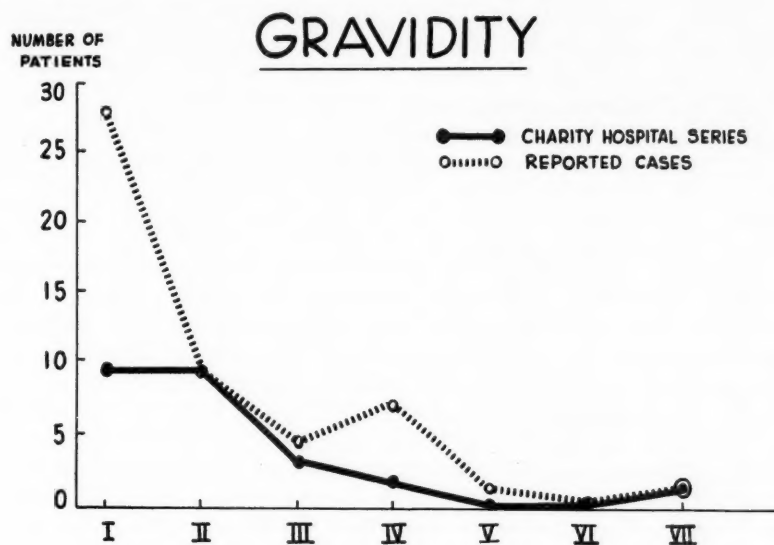


Fig. 2.

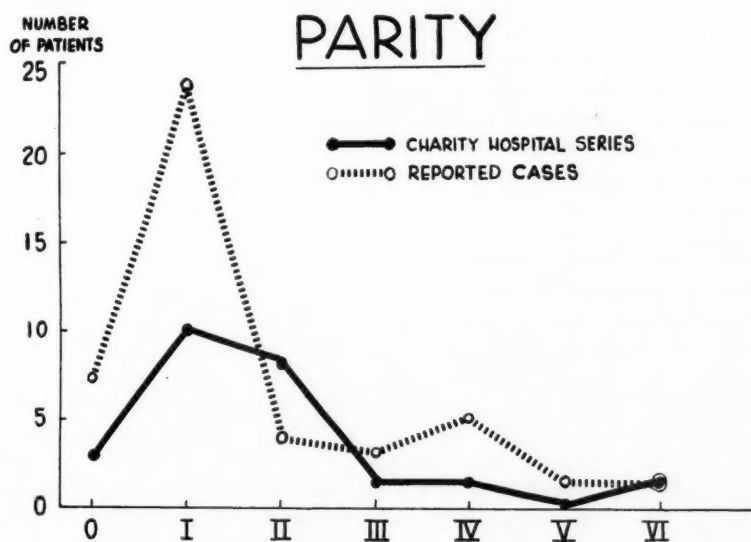


Fig. 3.

Symptoms and Signs.—The symptoms are so variable that Winsor and Burch⁴ have labeled S.C.D. "the great masquerader." Symptomatology may include weakness, fatigability, drowsiness, pain (abdomen, muscles, joints, chest, and head), dyspnea, palpitation, visual impairment, pallor, jaundice, fever

(low grade to septic), tachycardia, cardiac enlargement, abdominal tenderness, polypnea, variations in breath sounds, ulcerations or scars over malleoli, hepatomegaly, splenomegaly (early in the disease), epistaxis, hemoptysis, hematuria, cranial nerve palsies, coma, or convulsions. Individuals with S.C.D. may be remarkably free from all complaints for relatively long periods of time despite the persistence of a definite anemia. At unpredictable intervals there are exacerbations of the disorder which are associated with either a gradual increase in the anemia, or a rapid destruction of erythrocytes. Fever, increased icterus, abdominal pain, nausea and vomiting, and prostration may occur in "crisis" proportions. The acute symptoms are likely to persist for days. After such episodes several weeks are required for sufficient improvement to allow the patient to resume even a portion of her former activity.

Laboratory Findings.—Like many other disorders S.C.D. has no single laboratory finding which is in itself diagnostic. As we pointed out in a previous publication the interpretation of sickling tests is very important. One must be familiar with the morphologic variations which the cells may undergo; viz., crescent, holly leaf, oat, fish fin, or shattered glass shapes. One of the cases with a hematologic diagnosis of S.C.D. several years ago had to be excluded from this report inasmuch as follow-up studies revealed ovalocytosis.

The chief observable difference between the erythrocytes of S.C.T. and S.C.D. has been that a considerably greater reduction in the partial pressure of oxygen is required for a major portion of the former to sickle than of the latter. As pointed out by Sherman,⁵ a large proportion of the red corpuscles in the venous circulation of persons with S.C.D. are sickled, but comparatively few have assumed the sickle forms in the veins of individuals with S.C.T. However, experiments in vitro indicate that under sufficiently low oxygen pressure all of the cells of both types may assume the sickle shapes.

In the Charity Hospital series when well-developed symptoms were present there was usually an anemia of moderate to severe degree. The red cell count in Case 21 was 1,010,000. The lowest hemoglobin value was 2.5 Gm. Polymorphonuclear leucocytosis was present as a rule. When there was rapid hemolysis, as in "crisis," the count was often very high. In Case 19 it was 61,000. The bone-marrow picture associated with S.C.D. is that of hemolytic anemia plus sickle cells. An elevated index of icterus is present when the disorder is active, marked hyperbilirubinemia being associated with crises. Case 4 had a reading of 130.

Among the roentgenographic findings which may be present in S.C.D. are increased cardiac shadow (11 of 17 cases), osteoporosis, sclerosis, and trabeculation. Radiographic pelvimetric studies in 13 cases revealed a volumetric capacity of the transverse diameter of the midpelvis to be less than 550 c.c. in 7 cases. Six patients had anthropoid-type pelves. Electrocardiograms suggestive of myocardial disease were reported in 4 of the Charity Hospital cases. Two patients had definite electrocardiographic evidence of myocardial disease.

Indications for Sickling Tests.—Ideally, one would say that all pregnant Negroes should be given the benefit of a properly performed and carefully interpreted sickling test; however, since probably less than one in a thousand would have S.C.D., this is not practical in many localities. Certainly all obstetric patients are entitled to tests for anemia. If a Negro is found to be anemic, sickling tests are indicated. The presence of jaundice makes such procedures imperative. They should also be done in cases of sepsis (regardless of whether it is due to urinary tract infection or is of the postpartum or any other type), cases of suggestive S.C.D. history (abdominal or joint pains, leg ulcers, anemia, jaundice, weakness, dyspnea), and cases having bizarre symptoms. Some of the patients having fever of undetermined origin will prove to be victims of the sickle-cell disorder. If the sickling test proves positive, the patient is entitled to a complete hematologic survey.

Therapy

The management of patients in the latent or chronic phase is that of optimum obstetric care, with awareness of the fact that these patients are particularly susceptible to complications. They should be seen frequently during the antenatal period and every effort employed to improve their general state of health. Particular attention should be paid to their nutritional requirements, since most of them have faulty diets due to their economic status. Although there is at present no available therapeutic agent which is specific in the treatment of the anemia of this disease, we advise that iron and vitamins be given, inasmuch as an associated iron deficiency anemia may be present. One must be on the alert for detection of symptoms or signs which are indicative of S.C.D. activity or of a complicating condition. Fever, pain, excessive weight gain, decreasing hemoglobin, hypertension, pyuria, albuminuria, or hematuria, alone or in combination, constitute an absolute indication for immediate hospitalization and thorough investigation.

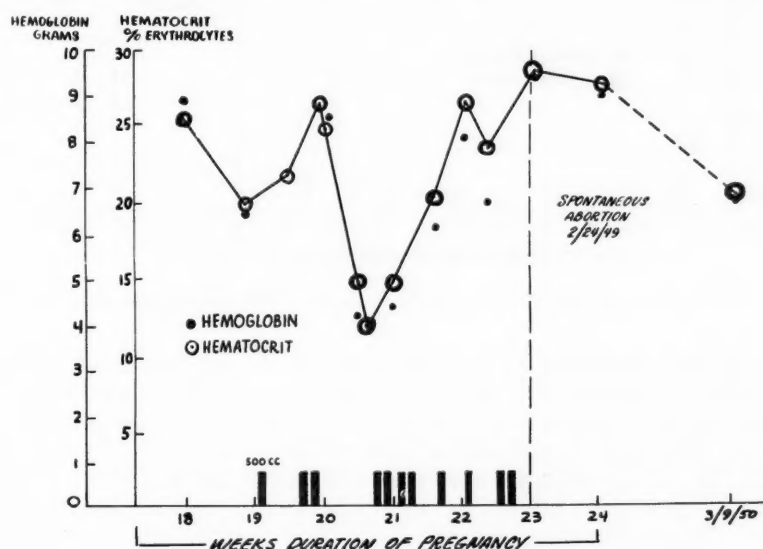


Fig. 4.—Transfusions of whole blood in Case 19.

It cannot be overemphasized that S.C.D. patients are very susceptible to infection and exhibit a poor tolerance to complications. In the Charity Hospital series urinary-tract infections were present in 46 per cent of the cases. The other complicating disorders included toxemia—22 per cent, respiratory infections—19 per cent, postpartum sepsis—19 per cent, syphilis—8 per cent, and tuberculosis—5 per cent. This study shows consistent improvement in the patients' condition, including anemia, after the complicating conditions had been controlled or eradicated.

The question of administering blood to patients with S.C.D. solely because of their low hemoglobin and erythrocyte figures has been prominent for years. After she had received a total of 5,500 c.c. of blood between the eighteenth and twenty-third weeks of pregnancy, the peripheral blood picture of Case 19 (Fig. 4) was essentially unchanged. During that time she had no bleeding until she aborted and very little then. It is interesting to compare the course of her anemia with that of Case 18 (Fig. 5) who had only one transfusion. Lund⁶ has been favorably impressed with the results which he obtained in Case 21 using transfusions of washed erythrocytes. We whole-

heartedly agree that blood should be given to S.C.D. patients for specific indications. Moderate anemia is not such an indication. A study of the patients in this series reveals that most of them were able to carry on practically full activity with a hemoglobin of 8 Gm. provided they had no complications. This is well correlated with the fact that 11 of these patients had an average of 9.6 Gm. of hemoglobin in a nongravid state free of complications.

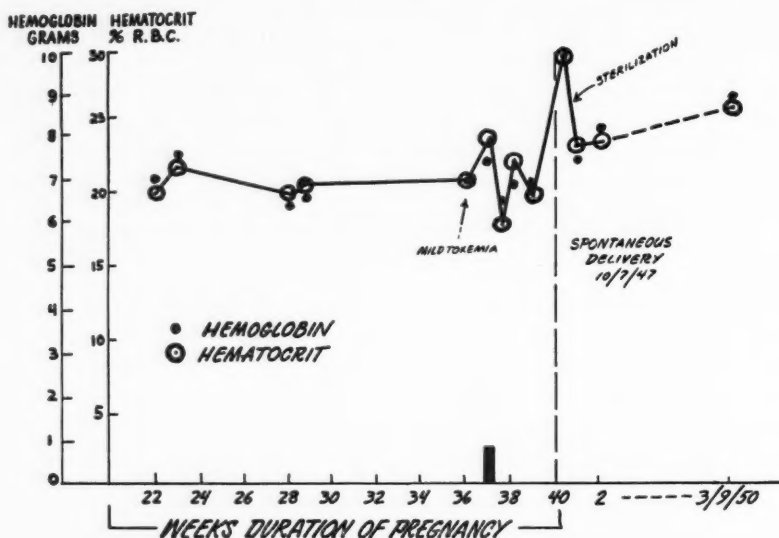


Fig. 5 (Case 18).—Course of the anemia without transfusions.

Just as severe anemia is an indication for blood administration, so is severe infection. Fig. 6 depicts the effect of infection on the circulating erythrocytes. It is our impression that the septic S.C.D. patients are more likely to improve with repeated transfusions. In certain cases it is deemed advisable to increase the blood volume immediately prior to delivery or operation. Obviously additional blood must be available then to prevent and combat shock as well as to replace blood excessively lost. The amount and the rate at which it is administered should be individualized. In instances of hemorrhage and circulatory collapse the rate may be rapid and the administration continued until a satisfactory blood pressure is regained and/or the blood loss arrested. However, some of these patients have circulatory impairment which necessitates slow administration in order to avoid excessive circulating blood volumes which may result in pulmonary edema. The majority of transfusions given during 29 of the 37 gestations terminating at Charity Hospital have been in 500 c.c. quantities. Some patients with dyspnea have been given 250 c.c. transfusions. Pyrogenic reactions have been more common than in many diseases but no death has occurred at that institution in an obstetric patient with S.C.D. which could be attributed to a blood transfusion. It has been suggested that blood free of sickling be given, but there has been no objective evidence to justify this. To the contrary blood has been transfused from healthy donors with S.C.T. to patients with S.C.D. and a normal survival time of the erythrocytes found.

Crisis.—Most of the Charity Hospital patients having crises have received oxygen therapy. Its effect has not been spectacular. Usually there is some decrease in dyspnea but pain has not been definitely diminished. The only satisfactory means of relieving pain has been the administration of analgesics

such as meperidine hydrochloride. Since one idea as to the cause of pain is thrombosis and since some of these patients develop thromboses and emboli as proved by autopsy, anticoagulants have been used. The experience as to their effectiveness has been so limited as to preclude proper appraisal. However, for Case 14 with postpartum femoral and saphenous thrombophlebitis heparin and Dicumarol administration resulted in dramatic relief. Further evaluation is indicated particularly in regard to the advisability of prevention of thrombosis.

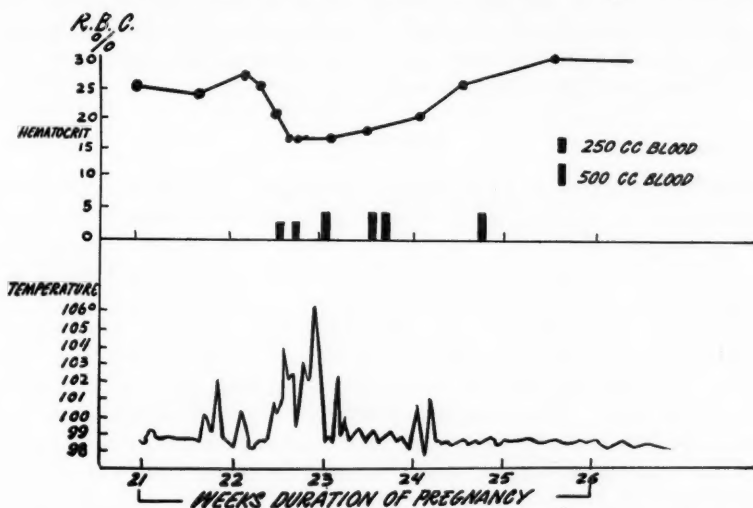


Fig. 6 (Case 4).—Effect of infection on circulating erythrocytes.

Most of the cases in crisis have received blood transfusions. Again we wish to emphasize that crises have usually occurred with associated disorders. The effort to cure or control such disorders appears to be the most effective means of aiding the survival or recovery of the patient. Since some patients with cardiac failure may be encountered, digitalization has been advocated. It is our belief that proper digitalization has no ill effects in S.C.D. patients and when there is doubt as to the presence of congestive heart failure they should be digitalized.

Delivery

Delivery should be conducted so as to avoid trauma, anoxia, blood loss, and infection. Local anesthesia has proved particularly desirable. Pure oxygen should be administered by mask during delivery. A needle should be in place, with an infusion proceeding slowly, so that blood can be readily administered if shock or excessive blood loss occurs. Eleven patients had spontaneous deliveries and a similar number were delivered by forceps extractions. Postpartum hemorrhage occurred once. Cephalopelvic disproportion was encountered in 3 of the 24 patients. One pregnancy was terminated by difficult forceps extraction, another by craniotomy, and the third by cesarotomy. Another laparotrachelotomy was done because of the impression that severe placental abruption existed in Case 24 known to have S.C.D. The erroneous diagnosis was made because the patient had continuous pain and rigidity of the abdomen associated with signs of fetal distress. The average total duration of labor was 14 hours, 15 minutes. There were 6 cases in which the labor exceeded 24 hours. The largest baby weighed 7 pounds, 10 ounces, and was delivered spontaneously. Because of the increased likelihood of infection the prophylactic administration of antibacterial agents is recommended.

The therapeutic termination of gestation has been employed for one case. In general, we presently advocate the termination of cyesis in patients with S.C.D. for the same accepted reasons as in those individuals without this blood disorder. However, with the sickle-cell condition remaining active, together with others which necessitate termination, interruption becomes more imperative. Although there have been no patients in whom it appears advisable to terminate pregnancy during the first trimester due to S.C.D. per se, it is likely that some patients with objective residual effects of the disease may be encountered in whom termination would be advisable. Particularly the residual effects in the nervous system such as feeble-mindedness, memory defects, and cranial-nerve palsy may be encountered.

Mortality

Four deaths occurred in this series. The first took place three hours after delivery following a prolonged labor with uterine inertia. The patient had received no prenatal care and was in very poor condition due to tuberculosis of the spine with iliopsoas abscesses. A caseous hilar lymph node was found. Although she had a major complicating disease and probably had S.C.D. over a period of years, as indicated by the 300-gram spleen, the pathologist did not deem the death directly due to S.C.D. since massive pulmonary thrombosis was present. The second death occurred in a case of prolonged labor with intrapartum infection. The patient received blood transfusions and chemotherapeutics. In her case the uterine and urinary tract infections were overwhelming. Her spleen weighed 1,180 Gm., indicating that her S.C.D. had not been active long. A review of this case causes us to list it as a preventable death. In 1947 a patient expired in an emaciated state shortly after delivery in spite of the administration of oxygen and blood. She had been rendered easy prey to sickle-cell crisis by a resistant pyelonephritis uncontrolled by sulfadiazine, penicillin, streptomycin, and ureteral catheter drainage. She developed bacteremia and pyarthrosis. Since termination of pregnancy to aid in the eradication of the urinary tract infection might have prevented the severe septic state, this death was probably preventable. The last death occurred in 1948 in a 25 weeks gravid patient admitted to the medical service acutely ill without having previously received attention during her pregnancy. She expired within 48 hours of admittance. No blood was administered. It is our opinion that this death was probably not preventable at the time the patient was admitted to the hospital. It is a matter of conjecture as to the role that heparin might have played, had it been administered.

Termination of Gestations and Fate of Offspring

The gestations in the Charity Hospital series yielded only 60 per cent surviving offspring. This is to be compared with the figure of 66 per cent in the literature (Table I).

TABLE I. TERMINATIONS OF PREGNANCIES

	CHARITY HOSPITAL SERIES	GROUP IN LITERATURE	TOTAL
Abortions	8 (16%)	14 (15%)	22 (15%)
Births after more than 27 weeks			
Live	30 (60%)	63 (66%)	93 (64%)
Stillborn	4 (4%)	6 (6%)	10 (7%)
Neonatal death	5 (10%)	6 (6%)	11 (8%)
Died undelivered	1 (2%)	5 (5%)	6 (4%)
Hysterotomy	1 (2%)	2 (2%)	3 (2%)
Salpingectomy	1 (2%)	0	1 (.7%)
Total gestations	60	96	146

The neonatal survival is shown in Fig. 7. Blood studies and follow-up examinations were recently performed on 28 of the children. Nineteen were found to have S.C.T. and 9 were nonsicklemic. No instance of S.C.D. has been discovered up to the present time. In perusing the literature we found a total of 31 reports concerning the offspring. Ten were positive for sickling and 21 were negative, but it must be pointed out that some of these determinations were done on newborns. We have made blood studies on the mothers of children having proved S.C.D. A number of these women do not exhibit sickling; consequently, the inheritance pattern is quite complex.

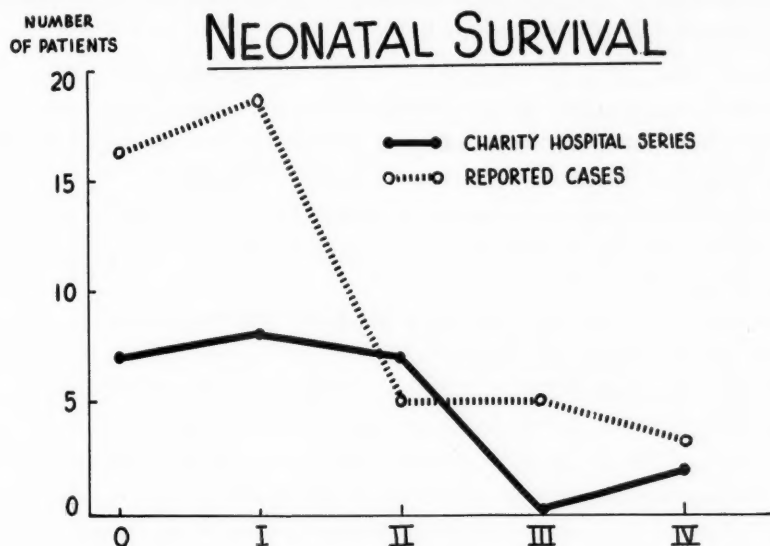


Fig. 7.

Present Status of Patients

Follow-up studies during March, 1950, revealed that 10 of the patients had a hemoglobin level of less than 10 Gm. One had a reading of 7 Gm. and is again pregnant. Another carries on normal physical activities with a figure of 7.5 Gm. Nine of the patients had hematocrits of less than 30 per cent. Seven had leucocyte counts of over 10,000. Eight had icterus indices of over 15. All cases showed 95 per cent or more sickling in 24 hours. Case 10 expired of pulmonary tuberculosis March 26, 1950. Case 13 was delivered in October, 1945, and is living in Texas. She has had no additional gestations and her activity is reported as normal. Case 17 was readmitted to a medical ward Nov. 11, 1947, and expired of cerebral infarction. Case 22 was delivered only a year ago and has moved to Mississippi. Her activity is said to be unrestricted. Case 24 has been delivered less than ten months and due to her mental status fails to cooperate.

Future Pregnancies

Since approximately one-third of the total of 50 gestations in these 24 mothers did not result in a living child and since some type of complication was encountered in all of the 37 observed gestations, future pregnancies offer a serious outlook. If there is objective evidence of impairments of circulatory, pulmonary, or renal function due to other disorders, the risk of pregnancy may be too great. Since these mothers usually die young (the eldest in this series is now 32), the question arises as to who will be responsible for the future care of their offspring.

In considering the ultimate fate of the children it is appreciated that there is an increased incidence of S.C.T. and a strong likelihood that some will develop S.C.D. Consequently, in the present state of knowledge, it is inadvisable for a person with S.C.T. to choose a mate who has S.C.T.

Summary and Conclusions

1. The incidence of sickle cell anemia or sickle-cell trait in Negro obstetric patients in New Orleans is approximately 8.3 per cent.
2. The incidence of sickle-cell disease in Negro obstetric patients in New Orleans is about 6 per 10,000 deliveries.
3. One of every five mothers with sickle-cell disease presently and previously reported has expired while classified as an obstetric patient.
4. Only approximately two-thirds of the gestations recorded in the literature and at Charity Hospital have yielded living offspring.
5. The manifestations of sickle-cell disease are so variable that one must be on the alert for the condition in order to make the diagnosis during the early stage of activity of the disease.
6. Sickling preparations should be properly made and carefully evaluated in the cases of all pregnant Negroes with anemia, jaundice, severe illness, or those with history or findings suggestive of the disease. If the test is positive, a complete hematologic survey is indicated without delay.
7. Patients with sickle-cell disease are particularly susceptible to complications. They exhibit a poor tolerance to infection.
8. The clinical course is closely correlated with the course of associated disorders.
9. Blood should be administered to sickle-cell diseased patients for specific indications including severe anemia, severe infection, and impending shock. It has resulted in only a temporary improvement in the peripheral blood picture when given solely to combat anemia.
10. Sickle-cell disease per se is not an indication for termination of gestation; however, associated disorders may tip the balance in favor of interruption of pregnancy.
11. The matter of sterilization is one for individualization, remembering with consideration of the facts that pregnancy has no beneficial effects on the disease and that most of the patients in the S.C.D. category do not live long enough to rear their children.
12. The victims of sickle-cell disease, in view of the final outcome, are entitled to optimum obstetric care. Early hospitalization and proper management of complications offer much to alleviate their suffering and prolong their lives.

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Discussion

DR. CARL BACHMAN, Philadelphia, Pa.—One of the many aspects of sickle disease and the sickle trait that has intrigued me has been the possible effect that sickling of maternal erythrocytes may have upon the welfare of the fetus in utero. As we already know, fetal and neonatal mortality rates are high among mothers afflicted with sickle disease. Most of this infant morbidity must obviously be due to such factors as maternal anemia, infection, and toxemia. But a substantial residuum must certainly be attributable to the thrombosing effects which sickling of maternal erythrocytes imposes upon the subplacental circulation.

Granted such a mechanism in the comparatively few mothers afflicted with sickle disease, it becomes important to examine for it in the much larger group of mothers exhibiting the sickle trait. In so far as sickling per se is concerned, the sole difference between sickle disease and sickle trait is one of degree, the former condition being associated with a marked and the latter with a minimal sickling tendency. It must be conceded that thrombotic phenomena are not noteworthy among individuals exhibiting merely the sickle trait, and that this condition is generally regarded as having little, if any, clinical significance. On the other hand, a similar lack of significance in obstetrics cannot be assumed unless the trait can be definitely shown to be harmless to the fetus by a careful check of the abortion, stillbirth, and neonatal morbidity rates of large numbers of mothers who show it. We all know how subtle and elusive the causative factors can be in many instances of fetal death in utero and in many premature births. To the best of my knowledge, no such study of the sickle trait has yet been made.

Since the incidence of sickle trait among Negroes is approximately 8 per cent, the finding of even a moderate elevation of fetal and infant mortality among such mothers—i.e., a rate of 10 per cent, or one that is roughly half that found in sickle disease—could alone account for 8 infant deaths per 1,000 births of all Negro infants. The question may not, therefore, be merely an academic one and, if its formulation makes any sense whatsoever, Dr. Beacham's clinic would appear to be the place in which to examine it.

DR. THADDEUS MONTGOMERY, Philadelphia, Pa.—The frequency with which sickle-cell anemia is encountered in a large obstetric and gynecologic service where there is a high proportion of Negro patients makes this an important complication in our field. While Philadelphia may be considered a northern city, yet we have a percentage of 80 to 85 of Negroes in the obstetric wards of the Jefferson Hospital, and almost 100 per cent in the obstetric and gynecologic wards of the Philadelphia General Hospital. Several reports have been submitted from our clinic by Dr. Hodges and Dr. Bernstine, and the number of cases which are observed is constantly increasing. Whenever a patient presents bizarre manifestations, we now think of sickle-cell anemia as one of the first possibilities. Particularly is this true in cases of sepsis and toxemia-like manifestations of pregnancy.

It may be pointed out that this is only one of the several phases in which considerable racial difference is manifested in obstetric and gynecologic patients. Nutritional deficiencies, rickets and deformities of the pelvis, frequent occurrence of cephalopelvic disproportion, increased frequency of fibroid tumors of the uterus, and especially of fibroid tumors complicated by pelvic inflammatory disease, fewer birth-tract injuries, are characteristic of the Negro, and constitute significant racial differences from the white.

DR. HOWARD TAYLOR, JR., New York, N. Y.—I have two points to raise on the basis of six cases of sickle-cell anemia in pregnancy which we have among our histories at the Sloane Hospital. These cases afford certain contrasts worth noting.

Prior to three years ago we had had two deaths from sickle-cell anemia and were accordingly convinced this was a very serious and perhaps usually fatal complication of pregnancy. In the last year, however, we have had four patients who went through their pregnancies without mortality or even serious difficulties. These four patients spent most of the later months of pregnancy in the hospital and had repeated transfusions. It is, therefore, our present view that these patients can go through pregnancy without great maternal risk and with a fair number of infants surviving if their treatment is meticulously carried out.

One has to consider, however—perhaps Dr. Beacham will comment on this point—that this is a hereditary defect. Recent work has, for example, suggested that the sickle-cell trait in the red cells appears when one chromosome carries the factor and sickle cell anemia as a disease occurs when both chromosomes carry it.

We can certainly tell a woman with sickle-cell anemia that she probably will not die during her pregnancy, but there is a question whether we should expect her to take even a small additional risk if the only result will be the perpetuation of what may be a serious hereditary trait. The question of interruption of pregnancy has, then, to be considered not only in relation to maternal risk but also with regard to hereditary character of this illness.

DR. KARL WILSON, Rochester, N. Y.—Dr. Beacham has partly answered the question I am going to ask. In our community the Negro population is not large and my experience is limited to a single patient but we have seen her often. She has been coming in regularly for ten years. She has been critically ill several times. She is a Negro woman who is not married and has been rather promiscuous. Every time she has come to the clinic two or three months pregnant we have advised interruption. Each time she has refused but she would come back later, having taken care of the problem herself but incompletely. We have seen her this way five times in ten years, and the last time we advised interruption and sterilization. She is now thirty-five years old. I should like to ask Dr. Beacham what we should be justified in doing in view of these difficult social circumstances, if she becomes pregnant again.

DR. JOSEPH L. BAER, Chicago, Ill.—Maybe Dr. Beacham would say a word concerning the racial purity of the women involved, or the degree to which their negroid blood has been altered by mixture with other types.

DR. BEACHAM (Closing).—In regard to the work done at the California Institute of Technology, Pauling and his co-workers stated that there is a quantitative rather than a qualitative degree between sickle cell anemia and sickle-cell disease. In 1944 Murphy and Shapiro reported the results of their studies on the sickling phenomenon, indicating that sickling is a property inherent in the susceptible corpuscle. It is generally agreed at the present time that the defect is an intra-erythrocytic one. In studying the offspring of patients having true sickle-cell disease at the New Orleans Charity Hospital we have not found a single case in which the child has proved to have the disease; however, in the course of time some of them may develop the condition. We have also conducted studies on the offspring of patients having sickle cell anemia. None of these have manifested sickle-cell disease. Similarly to the experience of others, we have not found a higher incidence of obstetric complications in sickle cell anemic patients than in the otherwise normal Negro obstetric patients.

In answer to Dr. Baer's question, it may be said that we are of the opinion that the condition is limited, with very, very few exceptions, to the Negro race.

Dr. Bachman and Dr. Taylor brought out an important fact when they stated that these patients are candidates for repeated hospitalization inasmuch as treatment or the lack of therapy spells the difference between success and defeat.

PROPHYLACTIC CHEMOANTIBIOTIC* THERAPY AND LOW CERVICAL CESAREAN SECTION IN POTENTIAL AND ACTUAL INFECTIONS†

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WHEN a low cervical cesarean section can be safely performed despite the presence of unfavorable conditions that invariably cause postoperative sepsis, obstetricians will have attained a long-sought goal. Studies of maternal mortalities¹ in the past twenty years have revealed that sepsis was the most frequent cause of death and, likewise, a factor in almost fifty per cent of the fatalities that followed the performance of cesarean sections. Changes in cesarean section techniques were frequently made during the past twenty-five years in order to reduce the high mortality from sepsis. The low cervical type to a large extent replaced the classical operation. However, postoperative sepsis continued to complicate the recovery of the patient, particularly when it was preceded by prolonged labor, many hours of ruptured membranes, many vaginal examinations, and previous manipulative attempts to deliver the fetus. With these conditions present, the transperitoneal cesarean was considered too risky, and some institutions preferred the cesarean hysterectomy. The latter had the disadvantage of sacrificing the uterus in a young woman. A revival of the extraperitoneal cesarean followed, but was not universally adopted. Many found it necessary to practice and perfect the technique on elective cases. To reach the uterus and extract the fetus, a most unnatural anatomic route must be taken. The peritoneal cavity frequently is inadvertently opened and the bladder, if not perforated or damaged during the operation, appears raw, denuded, and traumatized (Ricci,² Waters,³ Keetel and Randall⁴).

As the newer extraperitoneal cesarean techniques were being introduced, sulfonamide and antibiotic drugs appeared as potent bacteriostatic agents. As these drugs became available, morbidity and mortality from general and postoperative sepsis dropped considerably. Consequently, those employing either the transperitoneal or extraperitoneal techniques are now using chemoantibiotics when sepsis threatens recovery. If chemoantibiotics can prevent and combat sepsis, the operative procedure, when needed, should be the one that is least traumatic to the mother, and offers no technical difficulty. Thus, when sepsis is potentially or actually present and an abdominal delivery is deemed necessary, one may employ the low cervical section, and the use of chemoantibiotics

*This term will be employed with reference to sulfonamides and antibiotics which are frequently used together or interchangeably to supplement their effects.

†Presented before the Chicago Gynecological Society, Jan. 20, 1950.

becomes a real test of their ability to combat or prevent subsequent sepsis. The concept that chemoantibiotic drugs, when used prophylactically, would make the transperitoneal approach safer in the presence of possible sepsis had simultaneously occurred to many.⁵⁻⁹ While a definite number of contributors have indicated their confidence in these drugs when dystocia conditions are present, no one in this country has so far reported grossly infected and neglected cases treated with antibiotic drugs, and a low cervical cesarean section is indicated.

Clinical Material for Study

Since January, 1947, we have studied 100 low cervical cesarean sections performed in patients who were grossly or potentially infected. Prior to this study, these patients, by previously accepted standards, would have been subjected to the extraperitoneal section or a cesarean hysterectomy; or, if delivered vaginally, to a traumatic forceps, or craniotomy after death of the fetus. The limitations and conditions for this study were:

1. Only low cervical cesarean sections are included.
2. Potential infection was considered to be present when labor had lasted more than twenty-four hours and/or membranes had been ruptured more than twelve hours. None of these patients had fever.
3. Actual infection was considered to be present when, in addition to a defined, potential infection, there were clinical manifestations of sepsis such as intrapartum fever, chills, and purulent and foul amniotic fluid.
4. Neglected cases were considered to be those of prolonged labors managed by private doctors or midwives in the home, usually for more than twenty-four hours, with no record of rectal or vaginal examination except the word of the patient, and cases where attempts at delivery had failed. (There were five such cases.)
5. Acidosis, as a cause for febrility during the labor was determined by blood chemistry and urine studies. Cases in which acidosis was the cause of temperature elevation and when the prolonged length of labor was only borderline have not been included in the present series.
6. All failed forceps attempts that were followed by a low cervical cesarean were regarded as only potentially infected cases unless clinical signs of infection, as stated above, were present.

Chemoantibiotic Therapy

In this study of 100 cases, 92 patients received penicillin. The latter was combined with sulfonamides and streptomycin in 49 and 3 patients, respectively. Penicillin was used exclusively in 40 cases and sulfonamides alone in 8. The therapy was started in 54 patients preoperatively and, in the remaining patients, immediately postoperatively and long before any septic reaction had occurred. Sulfadiazine was the only sulfonamide used. This drug and penicillin, whenever possible, were given in standardized doses. It is known that sulfadiazine and penicillin pass from the maternal to the fetal circulation, this being a large factor in preventing infection in the newborn.^{10, 11, 12} Aqueous solution of penicillin was given intramuscularly, 40,000 units every three hours, and when single-dose prolonged-acting preparations were available they were also employed. As newer antibiotics with greater potency against the colon-typhoid group of gram-negative bacilli become available (streptomycin, aureomycin, Chloromycetin, etc.), they are being used, but their numbers are insignificant in this series.

Comment

One hundred patients either potentially or actually infected were delivered by the low cervical cesarean section. Indications for the latter are listed in Table I. These operations were performed in two hospitals. Seventy-three were delivered at the Cook County Hospital by a staff of twelve senior and associate attending obstetricians, as well as the resident staff. All of these patients were service cases who often presented varying degrees of anemia. Consequently, the blood bank services were used frequently and as freely as was deemed advantageous to the patient. The remaining 27 were private patients from the obstetrical services of the Mount Sinai Hospital and were delivered by five obstetricians. The over-all group of women studied contains a mixture of the white and Negro races, and many nationalities of different economic status. With many surgeons participating, the factor of individual superiority is eliminated because all patients recovered. The only consistent item in all patients was the prophylactic administration of chemoantibiotics.

TABLE I. BASIC INDICATIONS FOR CESAREAN SECTIONS

	NO. OF CASES
Uterine dysfunction (6 had borderline disproportion)	40
Disproportion	33
Constriction ring	16
Cervical dystocia	5
Pre-eclampsia with prolonged labor	2
Elderly primipara with prolonged labor	2
Malpresentation	2
Total	100

There were no maternal mortalities despite the unfavorable conditions that preceded the operation (Table II). There were, however, five infant deaths: three stillbirths and two neonatal deaths. Febrile morbidities in this study were reckoned by the usual standard of fever of 100.4° F. (38.0° C.), or more, in any two twenty-four hour periods postoperatively, excluding the first twenty-four hours following the operation.

TABLE II. RESULTS OF LOW CERVICAL CESAREAN SECTIONS WITH CHEMOANTIBIOTIC TREATMENT

	NO. OF CASES
Maternal deaths	None
Fetal deaths	5
Bladder injuries	None
Peritonitis	None
Intrapartum sepsis	47
Morbidity incidence	45

Table III is a comparison of the incidence of morbidity in our cases which had prophylactic chemoantibiotic therapy with that of a control group. The latter were a contemporary group of 201 patients who had low cervical cesarean operations at the same institutions. Their average morbidity incidence was 39.3 per cent. This group was divided into two groups, one of which had electively performed cesareans. The morbidity rate in this group was lowest of all, only 30.9 per cent. The nonelectively performed cesareans made up the other group and herein the morbidity rate was definitely higher at a 49.4 per cent level.

The patients comprising our study were also divided into two groups. Those who were regarded as only potentially infected totaled fifty-three. This group had labors and periods of rupture of membranes that ranged up to four

days. Two of them included a "failed forceps" procedure, but in all of them there were no signs of sepsis. Their morbidity level was 33.9 per cent and, like the group operated upon electively, no febrile reaction was noted for more than four postoperative days. The patients who had undeniable evidence of some sepsis prior to the operation were regarded as actually infected and this group of 47 cases had the highest level of morbidity, 57.4 per cent. However, postoperative morbidity incidence here was only 1.16 times higher than in the control nonelective groups, and in both these groups there were patients whose febrile period extended over many days. The governing factors that might influence the degree of morbidity are bacterial virulence, resistance of the patient to the invading microorganisms, and the resistance of the latter to the antibiotics. It is significant that no patient in our series exhibited any evidence of peritonitis or ileus.

TABLE III. A COMPARISON OF THE INCIDENCE OF POSTOPERATIVE FEBRILE MORBIDITIES

	NO. OF CASES	NO. OF MORBID- ITIES	NO. OF FEBRILE DAYS*							PERCENT- AGE MOR- BIDITY
			2	3	4	5	6	9	11	
<i>201 control cases (no chemoantibiotic prophylaxis).—</i>										
A. Elective cesarean sections	110	34	25	7	2	-	-	-	-	30.9
B. Nonelective	91	45	25	9	7	2	2	-	-	49.4
Total	201	79	50	16	9	2	2	-	-	39.3
<i>100 cases with prolonged periods of hours of labor and rupture of membranes (chemoantibiotic prophylaxis).—</i>										
A. Potentially infected cases	53	18	5	11	2	-	-	-	-	33.9†
B. Actually infected cases	47	27	9	10	4	1	1	1	1	57.4†
Total	100	45	14	21	6	1	1	1	1	45.0

*Temperature of 100.4° F. (or higher) not counting the first 24 hours of postoperative period.

†No postoperative peritonitis.

Considerable credit for the decrease in septic morbidities and mortalities following cesarean section must be attributed to the use of chemoantibiotics. While the virtues of the latter are being extolled, other factors that played a part in lowering the rate of infection must not be overlooked. Current improvements in anesthesia and operative technique, the health of the patient through better prenatal management, and, last (but quite important), the more frequent and safer use of blood transfusion have contributed indirectly to decreasing the incidence of sepsis. Adequate blood replacement, as needed because of hemorrhage or a severe degree of anemia, is a potent factor in the patient's postoperative recovery. It was, therefore, employed in 80 per cent of our series. Some of the patients, septic prior to the operation, had a more severe postoperative course and a longer average hospital stay.

When cases were analyzed from a viewpoint of the number of hours of labor, or by the period of time that membranes had been ruptured, the subsequent morbidity did not follow the expected pattern (Table IV). Whereas the morbidity incidence is expected to increase more or less proportionately with the hours of labor or hours of rupture of membranes, this was not apparent when chemoantibiotic therapy had been administered prophylactically. Our patients, for the most part, had a combination of both prolonged labor and many hours of ruptured membranes. All of the 3 patients who were in labor less than twelve hours had a long period of ruptured membranes and 2 of them had intra-partum sepsis. Further, we found that 49 women had membranes ruptured

more than twenty-four hours and, in 83 patients the labor was more than twenty-four hours. In 52 women, the length of labor ranged between thirty-six and one hundred thirty-two hours. Failed forceps preceded the operation in 5 cases and, in 2 of these patients, Dührssen's incisions had been made. Constriction ring was the basis for failure of the forceps to accomplish the delivery in 4 of these cases.

TABLE IV. DURATION OF LABOR AND RUPTURED MEMBRANES

HOOURS	LABOR NO. OF CASES	RUPTURED MEMBRANES NO. OF CASES
6-12	3	12
13-24	14	39
25-36	31	24
37-48	33	10
49-60	9	8
61-72	4	3
73 and over	6	4
Total over 24 hours	83	49

The following are brief abstracts of some of the case histories of actual infection encountered in this series.*

Case Histories

CASE 1.—L. B. S. was a Negro primigravida, aged 18 years, in labor 132 hours, with ruptured membranes for 60 hours. During this period, the cervix had dilated only 7 cm., and her temperature reached 102° F. Penicillin, 40,000 units, was administered every 3 hours after 40 hours of labor. A cesarean section was performed because the labor continued dysfunctional, and there was borderline contraction of the pelvis. A 6 pound, 13 ounce baby was delivered. The amniotic fluid was negative for bacteriologic cultures. The patient's temperature rose to 104° F. during the first 24 hours. She had bronchopneumonia, and there was a febrile morbidity for the next ten days. Penicillin, streptomycin, and blood transfusions were administered. The patient and baby were discharged 15 days after the operation.

CASE 2.—M. C., a 24-year-old para 0, was in labor 44 hours with membranes ruptured 32 hours. During this time, the cervix had dilated only to 4 to 5 cm. The fetus, presenting as a breech, exhibited distress but recovered when the mother was placed in Trendelenburg position and was given oxygen. The amniotic fluid became frankly purulent, and the patient had chills with a temperature of 101.4° F. Penicillin, 60,000 units every 3 hours, together with sulfadiazine, was administered 24 hours before the operation. An 8 pound, 13 ounce baby was delivered, and the patient had 3 days of febrile morbidity. Mother and baby were discharged on the eighth postpartum day.

CASE 3.—J. J., a Negro woman, had a prolapsed uterus. On admission, her pains were mild and the membranes had been ruptured 10 hours, the cervix, protruding through the introitus, was dilated 2 to 3 cm. Presentation was cephalic, plus two station. Prophylactic penicillin and sulfonamides were administered. After 128 hours of labor and 60 hours of ruptured membranes, it was noted that the amniotic fluid was definitely purulent and her temperature was 100.4° F. A cesarean section was then performed. A living female infant, weighing 6 pounds, 7 ounces, was delivered. Penicillin was continued for six days after the operation. The highest temperature was 100° F. on the second day. The patient was discharged on the ninth postpartum day.

*The first ten case abstracts are from the obstetric services of the Cook County Hospital, and the last two are from the Mount Sinai Hospital.

CASE 4.—J. B., a Negro primigravida, aged 21 years, had two convulsions prior to her admission. Labor pains had been present for 34 hours, membranes had been ruptured for 24 hours, and her blood pressure was 178 systolic and 110 diastolic. Stroganoff's management for eclampsia was instituted, but three convulsions occurred in the next twelve hours. After 54 hours of labor with the cervix dilated 8 cm., Dührssen's incisions were made. A constriction ring was found after two forceps applications had failed to deliver the baby. The cervical incisions were repaired and, later, chemoantibiotic therapy was instituted because of her 100.2° F. (rectal) temperature. Twenty-four hours later, with the constriction ring still present, a cesarean section was performed and a live baby weighing 10 pounds, 5 ounces was delivered. This patient was in labor for 76 hours and membranes had been ruptured 64 hours. There were six days of febrile morbidity. She was in the hospital thirty-one days because of a wound infection with some dehiscence.

CASE 5.—V. H., a Negro secundipara, aged 26 years, was admitted after labor of 85 hours, with membranes ruptured 12 hours, and a temperature of 100.2° F. The cervix was 8 cm. dilated and the station plus one. Dührssen's incisions were followed by a failed forceps attempt due to a constriction ring. The incisions were sutured and, after a 6-hour period of intravenous fluid and penicillin administration, a cesarean section terminated a labor of 91 hours and ruptured membranes of 18 hours. After a 15-day postoperative period with continuation of the penicillin administration, the patient was discharged with her baby after two days of febrile morbidity.

CASE 6.—L. M. A., a Negro primigravida, aged 27 years, was a short and squatty type, with a borderline pelvis. After 53 hours of labor and 26 hours of ruptured membranes, the cervix was only 3 cm. dilated. At this time the temperature was 101° F., pulse 110, and the amniotic fluid issuing from the vagina was foul and purulent. The fetal heart tones were believed to be satisfactory. Penicillin and sulfonamide therapy was instituted prophylactically. A constriction ring was found 4 cm. above the symphysis. The fetus, weighing 6 pounds, showed no sign of life when delivered by cesarean section. Although the patient developed a wound infection on the eighth day and had two days of low-grade febrile morbidity, her course was otherwise uneventful. She was discharged when the skin incision was satisfactorily healed, on the eighteenth postoperative day.

CASE 7.—P. P., a Negro primigravida, aged 23 years, was 10 hours in labor when admitted. The membranes ruptured on admission and her temperature was 100° F., then rose to 101.6° F. Penicillin therapy was started. There was little if any progress in the next 17 hours, and a cesarean section was performed with the cervix 5 cm. dilated after 27 hours of labor and 17 hours of ruptured membranes. An infant, weighing 7 pounds, 8 ounces, was delivered. A temperature elevation to 101.4° F. on the fourth day was the only febrile morbidity, and the patient was discharged on the twelfth day.

CASE 8.—V. H., a Negro primigravida, aged 35 years, supervised by a home delivery service, was in labor 35 hours with membranes ruptured 15 hours. When admitted, her temperature was 101.8° F. Intravenous fluids and penicillin were administered. Just before cesarean section was performed, her temperature dropped to 100° F. Duration of labor was 41 hours and membranes were ruptured for 21 hours. A 7 pound, 6½ ounce baby was delivered. Sulfadiazine was administered for the next 6 postoperative days. There were 2 days of febrile morbidity during that time. The patient left the hospital on the fifteenth day.

CASE 9.—F. P., a 34-year-old Negro, was in labor when admitted to the hospital and had a blood pressure of 164 systolic and 94 diastolic. The usual regime for toxemia was instituted. The uterine action was always dysfunctional. The membranes were ruptured artificially after 39 hours of labor. Progress was unsatisfactory and her temperature rose to 101° F. when labor had lasted 51 hours. Penicillin therapy was then started. Later, with 6-cm. dilatation, labor present for 57 hours and membranes ruptured 18 hours, a

cesarean section was performed and a 6 pound, 2 ounce baby delivered. The patient had no morbid course, and the penicillin and sulfonamide therapy was discontinued after the fourth postoperative day.

CASE 10.—H. S., a Negro woman, para i, had a borderline pelvis. She had had two vaginal examinations during 29 hours of labor at home. The membranes had been ruptured for 11 hours. The head could not be impressed beyond a minus one level. With two vaginal examinations under questionable asepsis, temperature of 100° F., and labor prolonged, penicillin therapy was instituted. Four hours later her temperature rose to 100.4° F., and a cesarean section was performed. An infant weighing 8 pounds, 1 ounce was delivered. On the second postoperative day, her temperature rose to 102° F. She had no other febrile morbidity.

CASE 11.—D. K., a white primigravida, aged 22 years, whose membranes ruptured spontaneously with onset of labor, was admitted to the hospital. Her pains were desultory and, after 24 hours, the amniotic fluid discharge was found to be purulent and had a foul odor. Her temperature rose to 101.6° F., and she was put on penicillin routine. A cesarean was performed when the patient's labor and ruptured membranes were of 32 hours' duration. The febrile morbidity reached 101.2° F. and 100.8° F. on the second and third day. The patient was discharged on the tenth day. The baby had pneumonia but was discharged at the end of two weeks in good condition.

CASE 12.—F. D., a white primigravida, aged 32 years, in labor 40 hours with membranes ruptured for 50 hours, had dysfunctional uterine action with a constriction ring and cervical dilatation of only 5 cm., when a cesarean section was performed. Where the uterus was opened, the amniotic fluid was found to be purulent. The intrapartum temperature was 100.8° F. Penicillin and sulfonamides were administered before and after the birth of the baby. The temperature on the second postoperative day reached 102° F. and, on the third day, 101.6° F. The patient and her baby were discharged on the tenth day.

One must acknowledge and give credit to the surgical resourcefulness of those who recently improved the technique of the extraperitoneal cesarean section. Without the aid of sulfonamide and antibiotics, the preferred procedure is a successfully performed extraperitoneal cesarean section. The associated, and not infrequent, error of penetrating into the peritoneal cavity and the occasional unavoidable genitourinary trauma (which hardly ever occurs with the low flap procedure) is a hindering hazard to a more universal usage of the extraperitoneal cesarean section. Since both transperitoneal and extraperitoneal sections, when supported by chemoantibiotic prophylactic therapy, appear feasible in spite of conditions that formerly caused postoperative septic mortalities, it is logical to prefer the surgical technique that is most simple. Now that modern chemoantibiotic prophylaxis makes the low flap operation safer in the presence of sepsis, this procedure, when indications are valid, can be used. It is hoped that this work will be continued by us and tested by others because further corroboration is needed. If our results are confirmed, it is then inevitably true that there is hardly any need for the extraperitoneal cesarean section and, certainly, the cesarean hysterectomy as a prophylaxis against sepsis should be completely abandoned.

If prophylaxis such as is advocated can make abdominal deliveries safer, it follows that the cesarean section rate might also be reduced. In the past, many obstetricians, fearing to allow a longer trial of labor in the presence of adequate pelvis or uncertain disproportions, performed abdominal deliveries with an inadequate trial of labor. The fear of longer labor and prolonged rupture of membranes with sepsis complicating a cesarean section has cut the adequacy of the trial of labor. By no means should there be a lowering of any of the prevailing standards. Although these useful drugs make for greater safety,

valid indications for performance of a cesarean section must still be rigidly adhered to, and carelessness in surgical technique by no means should be countenanced.

Summary and Conclusions

1. One hundred low flap cesarean sections were performed on patients who had prolonged labors and many hours of ruptured membranes. Fifty-three of these patients were considered to be potentially infected and forty-seven were actually infected. The recovery of all patients was essentially due to chemo-antibiotic therapy. We believe that the low flap cesarean operation, because of its ease in performance and freedom from surgical complications, is ideal.

2. Blood transfusions and any other vehicle for bolstering the patient's resistance are of tremendous value. Eighty per cent of our patients received whole blood transfusions at time of operation or immediately postoperatively.

3. Although sulfonamides and penicillin are invaluable against development of sepsis, the indications for cesarean section must still be only those that have hitherto been considered as valid.

4. If future contributions confirm the findings of this report, there will be little if any need for the extraperitoneal cesarean section and cesarean hysterectomy should have no place as a prophylactic procedure against sepsis.

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25 EAST WASHINGTON STREET

Discussion

DR. JAMES E. FITZGERALD.—In a monograph on cesarean section, Franklin S. Newell makes the following remarks: "The great majority of patients who present indications for cesarean section can be divided into two groups, the favorable and the unfavorable. For a patient to be classed as favorable certain conditions must be fulfilled: (1) There must be no suspicion of uterine infection; (2) she must not show signs of exhaustion, whether general or uterine, from any labor which may have occurred; and (3) there must have been no attempt at operative delivery from below. That definite uterine infection should be an absolute contraindication to cesarean section, unless the operation is completed by removal of the uterus, is generally conceded, since the retention of the infected uterus often results in fatal infection no matter whether a classical or extraperitoneal operation be performed."

In the last (1945) edition of his textbook Stander in discussing contraindications for cesarean section made some observations which may have by-passed your memories. He said: "In our clinic (New York Lying-In) Douglas carried out bacteriologic studies in over 500 patients at the time of cesarean section. He obtained cultures from the intraovular space after extraction of the child as well as from the lower uterine segment after removal of the placenta. His bacteriologic findings, correlated with the clinical results, clearly show that a cesarean section performed prior to labor is relatively safe; that during the first eight hours of labor, particularly with the membranes intact, the hazards are only slightly increased, but that after twelve hours of labor the risk from infection increases definitely and progressively with each hour of labor. From a bacteriologic point of view, cesarean section is contraindicated in patients who have been in labor for twelve hours or longer and particularly if the membranes are ruptured. In such cases should cesarean section be the only available method of delivery, an extraperitoneal or radical Porro operation should be performed with the full knowledge that the risk of the mother is increased."

Apparently we have come a long way since 1945. Whether we have proceeded in the right direction, or at a safe speed may be open to question.

In 1930, the maternal death rate in Chicago was 4.7 per 1,000 live births. It has declined continuously since then and in 1948 and 1949 it was well under 1 per 1,000—a striking proof that the factors mentioned by the essayists have decreased greatly the hazards of pregnancy.

I have watched with deep interest the work which is the basis for the report just given. I can in no way condone the apparently atrocious obstetrical judgment which resulted in cases that were salvaged by somewhat heroic measures. Nevertheless it is extremely gratifying to know that cases formerly considered beyond the hope of safe operative intervention may be offered such benefits with apparent safety.

Sound obstetrical judgment and proper timing would have prevented many operations done in the presence of infection noted in the essayists' presentation.

I believe that it is wrong to teach residents that they may substitute penicillin for good obstetric judgment, and I am convinced that the present series notwithstanding its excellent results, is too small to contradict the old idea that it is better and easier to stay out of trouble than to get out of it.

DR. RALPH A. REIS.—This report offers proof that neglected, mishandled, and infected women in labor can, with the aid of "chemoantibiotics," survive low cervical cesarean section. The essayists have shown once again that active chemotherapy and active antibiotic therapy will control obstetric infections, will make the low cervical cesarean section relatively safe in the presence of such infection, and will render extraperitoneal cesarean sections and cesarean hysterectomies unnecessary for the infected gravida.

I would request a further definition of the phrase "potential infection." If accepted as given in the paper, i.e., 24 hours of labor or 12 hours of ruptured membranes, it would include over 25 per cent of the patients on our service and would, therefore, seem too all inclusive. In passing, may I object to the term "potential infection" by any definition. It would seem wiser to group clinically all gravidas into "infected" or "clean." The opening statement that "unfavorable conditions which invariably cause postoperative sepsis" has fortunately not been our invariable experience.

The essayists have stated that "chemoantibiotic therapy was started in 54 patients preoperatively and in the remaining patients immediately postoperatively and long before any septic reaction had occurred." They then cite 12 patients all of whom had intrapartum sepsis before any therapy was instituted. They lay claim to 47 infected patients. Did these 47 become infected after chemoantibiotic therapy was instituted? Did the 53 potentially infected patients become potentially infected after the onset of chemoantibiotic therapy? I confess that I am confused.

DR. A. F. LASH.—Not only is it a question whether the patient lives and survives the infection but how much of a cripple or invalid she becomes thereafter, and how often do

we find a frozen pelvis that makes that patient sterile thereafter. I would like to know about these 100 cases six weeks after they left the hospital.

I should like to mention an experience of a few months ago when I did a second elective cesarean section on a woman 26 years of age who came to the hospital with the history of having ruptured her bag of waters at 6:30 P.M. She entered the hospital at 7:40 P.M. and by the time we got her to the operating room it was 10:30 P.M. and she was not in labor. Section was done under local anesthesia. There was some spillage of the remaining amniotic fluid which contained vernix and a little meconium was lost in the peritoneal cavity. Thirty-six hours later the patient appeared normal but vomited. Because of the vomiting we started her prophylactically on penicillin, 300,000 units daily. Twenty-four hours later or the third day postpartum her temperature was 104° F. pulse 120. The vomiting was partly overcome by means of the Levine tube. She was given streptomycin and penicillin. This temperature continued until the fourteenth day. On examination a bulging cul-de-sac was found, and on the eighteenth day post partum a colpotomy was done with the evacuation of some 300 or 400 c.c. of foul-smelling pus which contained colon bacillus. She made an uneventful recovery. When seen six weeks later she had a thickened parametrium and a vaginal discharge secondary to chronic cervicitis.

DR. H. CLOSE HESSELTINE.—We have had the good fortune at the Chicago Lying-in Hospital to have had over 19,000 deliveries with but six deaths in the last five years. We have not had a puerperal sepsis death since 1938 which represents over 38,000 consecutive deliveries. The incidence of neglected and mismanaged cases at the essayists' institution will be higher than at other hospitals in Chicago, a factor that they cannot control. This factor makes this study possible and justified.

I feel this kind of study is important but it is not important for all of us to do it. It is hazardous and dangerous. Actually every patient who goes into labor is potentially infected. From a bacteriological viewpoint every patient in labor or delivered has a bacterial invasion of the uterus. The bacterial content increases with prolongation of labor and continues for the first few days after delivery.

DR. FREDERICK H. FALLS.—Not many of us are faced with the care of infected patients as seen by Dr. Kobak and his associates at the Cook County Hospital. This is because, long before they have reached this dangerous condition, a decision has been reached as to what should be done and procedures carried out at a time when the management is relatively safe, but in these neglected cases the weight of authority is against doing low cervical cesarean section and in favor of craniotomy, Porro cesarean section, or extraperitoneal cesarean section. It takes a lot of moral courage to defy authority and to attempt to save these babies' lives, and at the same time retain the mother's uterus by doing a low cervical cesarean section and relying on antibiotics and drugs to prevent the spread of a fatal infection.

The authors have accepted this challenge and have proved that the operation is safe in 100 cases. Nobody in this Society, as far as I know, has had the nerve to do this.

DR. KOBAK (Closing).—This study may be regarded as being in line with a newer trend that is developing in the management of those cases having prolonged labor with a long period of ruptured membranes, but which nevertheless need a cesarean section. These patients might be parturients primarily mismanaged, or they might be women referred to our services after a long labor, or patients referred to us in our capacity as consultants. As Dr. Reis stated, we now can resort to the low cervical cesarean section if a cesarean should be indicated, and know that it is as safe as the extraperitoneal or a cesarean hysterectomy, when chemotherapy and antibiotic medication have been applied. Perhaps he may be technically correct in his objection to the term "prophylactic." However, I most emphatically differ with his concept of the so-called "potential infection group" included in this study. As stated in the paper, our patients were regarded as potentially infected when labor was *more* than 24 hours long and/or membranes were ruptured *more* than 12 hours.

The paper which he tells us he "read and reread" states that "this group had labors and periods of rupture of membranes that ranged up to four days. Included were two instances of failed forceps procedure but, in all of them, there were no signs of sepsis." Cases of this sort Dr. Reis would call "clean" but I still regard them as potentially infected and that is what they are labeled by some contributors to our obstetrical literature.

The critical comment about patients who did not receive antibacterial medication before the operation is understandable. There were certain patients seen in the early phase of our study who were just potentially infected and there were some patients admitted to our services already many hours in labor. In these other cases the medication was actively administered immediately after surgery and before the advent of postoperative sepsis, and in that sense they were prophylactically treated. All patients actually infected received chemoantibiotic therapy before the performance of the cesarean section.

The treatment of actually infected cases, including the five parturients who were referred to our services with evidences of intrapartum sepsis after many hours in labor at home, needs further reflection. As far as we could determine by study of the literature, no one had heretofore tested his faith in chemoantibiotic therapy as we did in instances where patients were grossly infected. With no previous precedent to guide us it seemed preferable in certain instances to defer temporarily the operation in order to bolster the patient's resistance by chemoantibiotic administration, blood transfusion, fluid administration, etc.

Dr. Lash inquired into the later course of these patients. Almost all of them from the Cook County Hospital services were examined six weeks after the operation and their condition was no different from that of the other puerperal women.

Although many new antibacterial agents have recently been described, penicillin is still the best of them all. Its only weakness pertains to the colon-typhoid group of gram-negative bacilli. In so far as most septic patients have more than one species of bacterial antigens to contend with, it is expedient to use penicillin complemented with sulfonamides or streptomycin or both. The future may change this. We are continuing this work with more and more confidence and we hope that others will try to verify our finding that chemoantibiotic therapy makes low cervical cesarean sections safe in potential and actual infection.

**EPIDERMOID HETEROPLASIA (HETEROLOGOUS EPIDERMOID
DIFFERENTIATION) OF BASAL CELLS OF ENDOMETRIUM
VERSUS SQUAMOUS-CELL METAPLASIA**

With the Report of a Case of Cholesteometra*

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(From the Pathological Department of the Woman's Hospital)

PERHAPS one of the greatest achievements of Robert Meyer was the contribution which he made to explain and clarify the process of healing of cervical erosion.¹

After extensive studies on a large histologic material, by method of topic reconstruction of serial sections on numerous specimens of cervical erosions, he arrived at the conclusion that the process of the final relining of the eroded surface of the vaginal aspect of the cervix by stratified squamous epithelium is not a metaplastic transformation of columnar epithelium.

He offered another and a very simple explanation, based, however, upon true histologically established facts and not upon vaguely understood assumptions of process of metaplasia.

Robert Meyer was able to establish that the process of healing of an erosion is a chain of events, which goes essentially through three stages:

The first stage (ulcerative stage) is characterized by a complete loss of surface epithelium, which is replaced by granulation tissue. The latter may form more or less prominent and more or less irregular fungating projections, which, in course of the process of healing, could be and usually are complicated by irregularly contoured depressions, of varied size and depth, produced largely by retraction of granulation tissue in the process of scarring.

The next stage of the erosion (glandular erosion) presents an attempt at initial epithelization of the granulating surface of the ulcerative erosion. The epithelium covering the fungating projections of granulation tissue is columnar and reveals almost always a tendency to form glandlike invaginations alternating with fungating projections of granulation tissue and vaguely imitating the racemose shape of typical cervical glands.

In the final stage of healing, the stratified squamous epithelium is not formed from the columnar epithelium by the process of metaplasia.

As the inflammation subsides, the stratified squamous epithelium (according to Meyer) begins to advance from the margin of the erosion, undermining the columnar epithelium and lifting it up from the underlying tissue. Doing so, the stratified squamous epithelium follows in a very exact fashion the outer contours of the glandlike and of the frankly glandular invagination, which were formed previously by the columnar epithelium in the process of the initial epithelization of the eroded area. This peculiar behavior of stratified squamous epithelium (in the third stage of the erosion) in its effort to regain its lost

*Proposed designation for distention of the cavity of the uterus by lamellated strips and debris of cornified epithelium with cholesterol crystals, following so-called ichthyosis uteri.

position on the vaginal aspect of the cervix must result and actually does result in the creation of rather irregularly contoured, club-shaped invaginations of stratified squamous epithelium of varied size, varied width, and varied length.

The irregularity of contours and the bizarre shape of invaginations of stratified squamous epithelium are easily understood, if we accept the conception of Meyer, that the essential process is a simple replacement of one type of epithelium (the columnar) by another (the squamous), and not a metaplasia.

The diversity of shape and contours of the stratified squamous epithelium is due essentially to the peculiar properties of the original terrain of the glandular erosion, which is characterized, as it was mentioned before, by manifold irregularly indented and inflected glandular invaginations of varied length, shape, and width.

Naming this rather simple process of replacement of columnar epithelium of glandular erosion by stratified squamous epithelium, epidermization of cervical erosion, Meyer entertained particularly the ambition to eliminate by such simple demonstration of histological facts, two factors which were and still are the source of confusion and error in the problem of correct diagnosis of carcinoma of cervix.

One of these factors is the myth of process of metaplasia, which implies rather obscure mechanisms, which are operating in the transformation of one cell type into another.

The heavy stigma of mystery enveloping such transfiguration of cells and tissues was and is responsible for a very suspicious attitude toward any irregularity of tissue patterns which may be produced in the course of the ill-understood phenomena of metaplasia.

The other factor, particularly leading to frequent diagnostic error, is the assumption that the invaginations of stratified squamous epithelium which arise in the final stage of healing of an erosion present essentially an invasive neoplastic proliferation of the epithelium.

Therefore, the process is regarded as surely precancerous, or even frankly cancerous, depending upon how diverse and irregular are the tissue patterns produced by the epithelial invaginations.

Instead of being suspicious if considered as a product of metaplasia, the epithelial patterns produced in the final stage of the cervical erosion are expected to be irregular and as complicated as they are, if we follow the explanation given to this process by Meyer.

Also, the downward growth of the stratified squamous epithelium, being an essential part of the process of healing of an erosion, as demonstrated by Meyer, does not represent, by any means, a true histological example of an invasive process.

Hence, while Meyer's explanation predicts and preconceives the irregularity of contours, the bizarre configurations, and the downward growth of stratified squamous epithelium as essential elements of a process of restoration to normal, a diagnostic difficulty with a tendency at least toward suspicion of malignancy is inevitable, if the process of healing of an erosion, in its final stage, is considered as an act of metaplasia.

The process of epidermization of cervical erosion as demonstrated by Meyer is not, by any means, an example of a transitory phase in a process of progressive development of a pathological phenomenon (metaplasia) with an uncertain outcome.

On the contrary, the process of epidermization is an ultimate restoration to normal, a final event in the chain of several phases of a process of regeneration

of tissue after a previous injury. Even though the process of epidermization manifests itself in a rather distorted fashion, it is final in the sense that it does not possess any progressive tendencies with an outcome of uncertain nature.

In a more recent paper² devoted to the discussion of histological diagnosis of carcinoma of cervix, Meyer complained that even today occasional errors of diagnosis are made particularly because epidermization is often erroneously called "metaplasia." This conception is, according to Meyer, fundamentally wrong and is based on noncritical judgment of single slides instead of a series of reconstruction.

One of the most influential opponents of Meyer in the problem of epidermization vs. metaplasia was Kaufman,³ who considered that even the heterotopous (buried below the surface) findings of stratified squamous epithelium originate from the columnar epithelium of the surface, which grows downward and which is subsequently converted into stratified squamous epithelium.

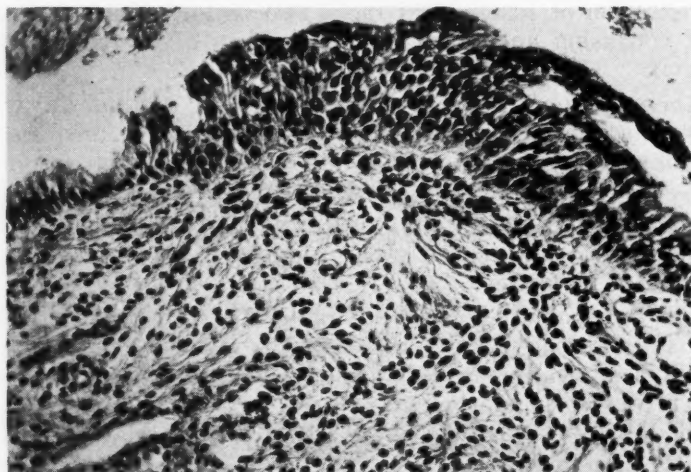


Fig. 1.—P. N., W.H.77248. Segment of a glandular papillary erosion of cervix. Isolated patch of epidermoid heteroplasia. The columnar epithelium is lifted up by epidermoid overgrowth of basal cells.

Kaufman stated that the most important reason for metaplasia of single-layered columnar epithelium into a stratified squamous epithelium is the deep down rooted metamorphosis of the subepithelial matrix tissue (*Mutterboden*). The columnar epithelium could not continue its existence after the transformation of the subepithelial succulent, loose, delicate connective tissue into a scorched, dried-out, firm tissue.

According to Kaufman, particularly in his conclusive statements in regard to the topic origin of carcinoma, originating simultaneously at different points (multicentric origin) due to the influence of unknown injurious agent, both the surface epithelium and the glandular epithelium represent single parts of the same continuous complicated epithelial surface plane.

If the surface epithelium prior to the attack by the carcinogenic agent has been already metaplastically converted into stratified squamous epithelium, the carcinoma formed in this area takes its origin from a cell complex which is composed of two essentially different type of cells, not unlike a rug composed of numerous two-colored squares.

According to Meyer, a finally developed columnar epithelium does not yield any more stratified squamous epithelium and vice versa.⁴

The potential source of columnar epithelium and stratified squamous epithelium are numerous islands of so-called "basal cells" whose existence beneath the surface epithelium and beneath glandular epithelium (particularly of the cervix) was established by investigations of Meyer.⁵

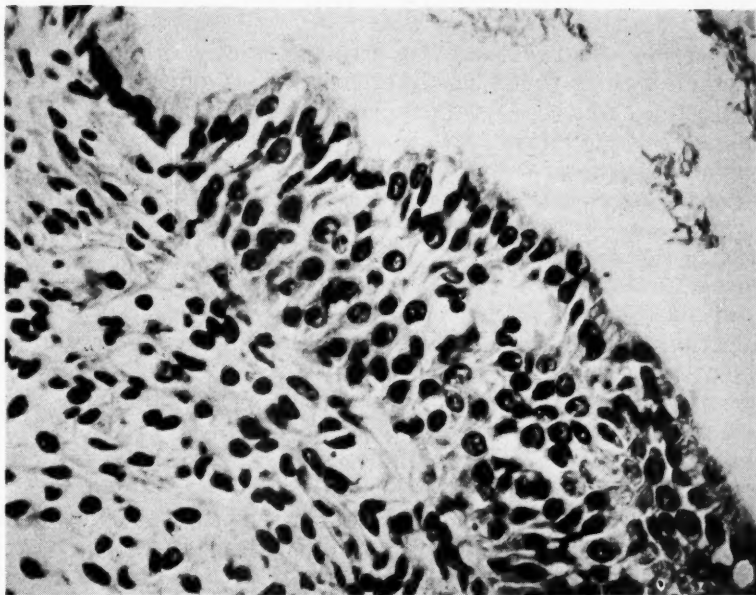


Fig. 2.—Same as Fig. 1, high power. Note the various shapes and sizes of the cells. They are representing various stages of epidermoid differentiation which is not complete at the present.

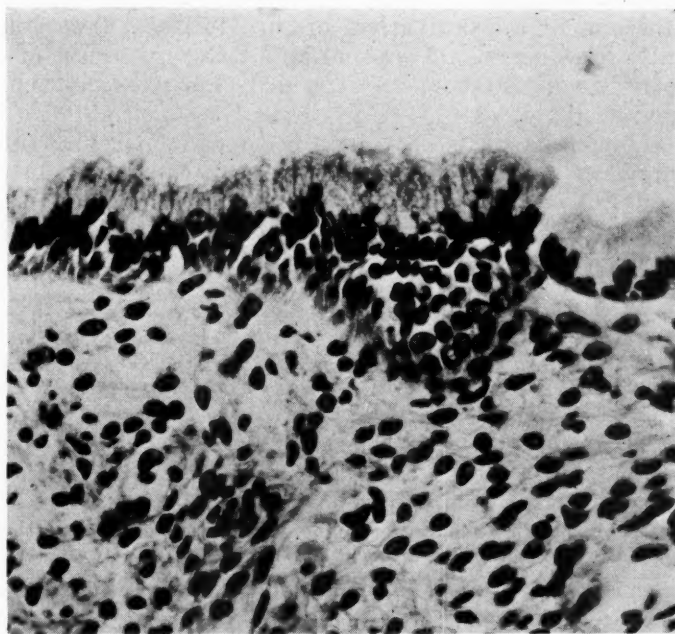


Fig. 3.—Same as Fig. 1. Isolated patch of beginning epidermoid differentiation of basal cells (which could easily be confused with round cells in this stage of differentiation). Note necropyknosis of the cells of columnar epithelium, which will be replaced by the epidermoid overgrowth of the basal cells.

The morphological differentiation of the basal cells is controlled by the functional requirements of the respective site of the body.

However, in abnormal conditions, the morphological differentiation of the basal cells may follow manifold patterns, which represent the histological expression of the inherent manifold potential properties of these cells (Figs. 1, 2, and 3).

It is debatable whether there are two essentially different types of basal cells or whether both variants of differentiation of epithelium (the columnar and the stratified squamous) arise from one only cell of origin.

In the process of normal embryonic development and in the process of normal constant regeneration of surface epithelium, the stratified epithelium of any kind (not necessarily squamous) arises from the basal cells. Primarily one single row of cells is followed by a later development of several rows of cells (stratification).

According to Meyer, this is a process of differentiation of cells and not an act of metaplasia.⁶

Stratification of columnar epithelium has many examples in normal histology. The uterus may not be an exception.

The out-of-ordinary presence of squamous epithelium in the uterus is not sufficiently convincing to justify the assumption of a process of metaplasia. It is merely an act of heterologous differentiation of epithelium for this respective site (organ) of the body.

Even the isolated areas of epidermization in the higher levels of the cervical canal, or in cervical polyps, or anywhere else within the realms of the mucosal lining of the derivatives of the Müllerian duct, do not represent a product of metaplasia.

All these incidences of seemingly ectopic stratified squamous epithelium could be explained by heteroplastic development of basal cells.

The conclusions reached by Meyer in regard to ectopic findings of stratified squamous epithelium in the derivatives of the Müllerian duct influenced us in histogenetic interpretation of an unusual and rather rare case of a progressive replacement of the endometrium by stratified squamous epithelium, observed through a period of five years.

At first, a few isolated foci of stratified squamous epithelium only were found accidentally in material obtained by curettement of the cavity of the uterus.

Five years later, the entire endometrium was completely replaced by stratified squamous epithelium.

Case Report*

Mrs. E. G. (61571, 46388, Woman's Hospital) was first seen on March 12, 1936. She complained, at that time, of moderately severe menopausal symptoms. Her last regular menstruation occurred around the middle of January, 1936. She had started to spot again about two weeks before this visit and continued to bleed scantily until one morning, when the normal menstrual flow started. Sometime in December, 1935, she had had urinary frequency and urgency, at which time a catheterized specimen of urine showed the presence of many pus clumps with a moderate number of free leucocytes together with a heavy trace of albumin.

Physical examination in March, 1936, did not yield anything remarkable except for a moderate generalized obesity. The gynecological examination revealed a uterus irregularly enlarged to that of about eight weeks' pregnancy, and of firm consistency. A large cystocele and a small rectocele with relaxation of the perineum were found at this time.

*The history and operative record are kindly contributed by Dr. Maurice Rashbaum.

The patient was married at the age of 26 years, had had three pregnancies but only one living child, who was at the time of her first visit 18 years old. Two spontaneous abortions without complications or sequelae followed, the last one about seventeen years ago.

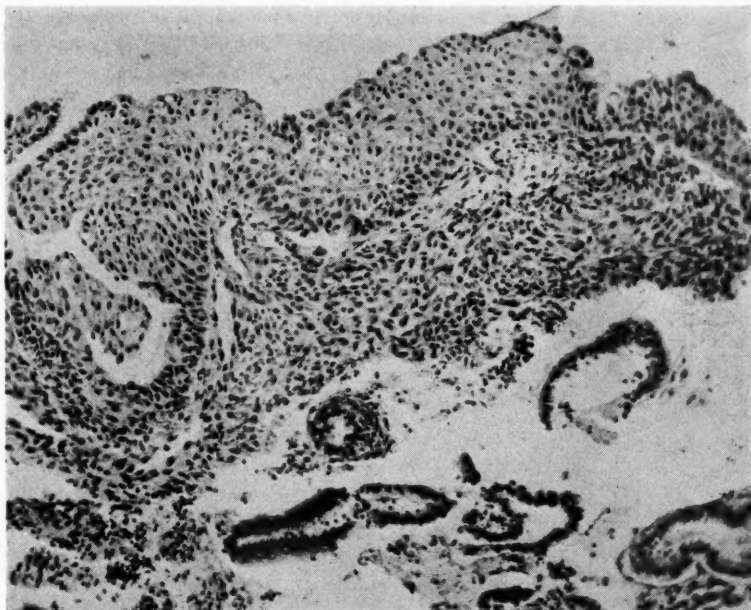


Fig. 4.—P. N., W.H.46388. Endometrial curettings. Epidermoid differentiation of surface epithelium of endometrium. Epithelioid change of stroma (endometritis).

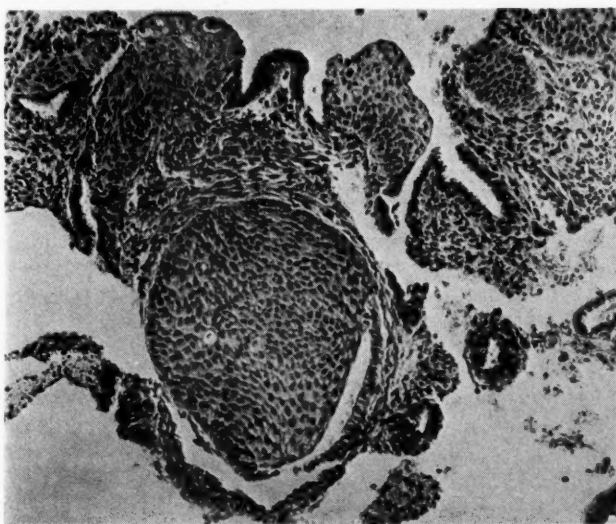


Fig. 5.—P. N., W.H.46388. Endometrial curettings. Stratified epithelium extending and growing down along and outside of the glandular epithelium. Isolated focus in the deeper portions of the tissue (pseudoinvasion). The stratified epithelium is squamous but not cornified.

On March 29, 1936, dilatation of cervix, curettage, and insertion of 100 mg. of radium for 18 hours (1,800 mg. hr.) were done at the Woman's Hospital (P. N. 46388). Microscopically, the endometrium was found in a state of secretion with mild glandular hyperplasia of the basal layer and edema of stroma.

Most striking were the findings of isolated foci of stratified epithelium on the surface of the endometrium. In several areas the epithelial cells were piled upon each other, forming five and in some instances as many as eight layers. Instead of a customary columnar shape, the individual cells were distinctly flattened, or polyhedral with faintly stained, round, vesicular, or oval nucleus. (Figs. 4, 5, 6, 7).



Fig. 6.—P. N., W.H.46388. Endometrial curettings. Isolated patch of stratified surface epithelium (beginning epidermoid differentiation).

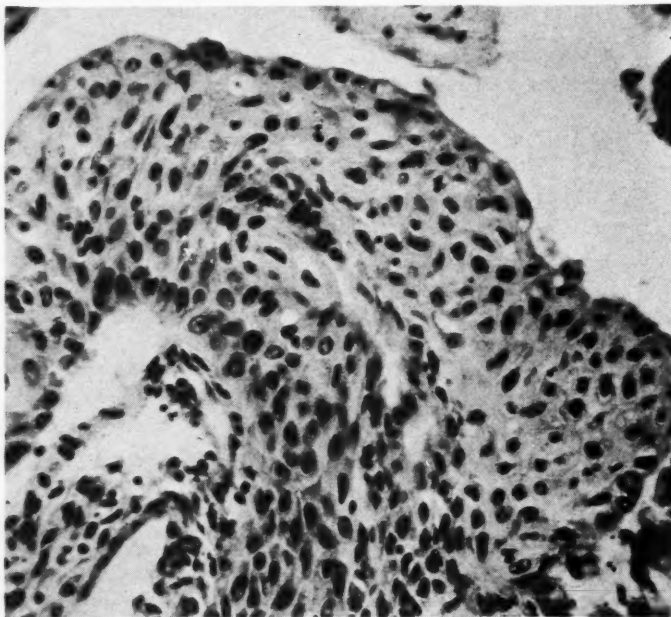


Fig. 7.—Same as Fig. 6, high power. Note the incomplete epidermoid differentiation of stratified epithelium. The state of differentiation is not unlike that of "carcinoma in situ."

The stroma underneath the stratified epithelium exhibited a swelling of individual cells assuming a more or less distinct epithelioid appearance. Lymphocytic infiltration with only a few polynuclear leucocytes was found among and around the epithelioid cells of the endometrial stroma.

Diagnosis: 1. Endometrium in secretory phase with mild basal glandular hyperplasia and edema of stroma. 2. Squamous-cell heteroplasia of surface epithelium of endometrium; and epithelioid changes in the underlying stroma (chronic endometritis).

The patient was subsequently seen at fairly frequent intervals complaining of menopausal symptoms, urinary frequency, urgency, and occasionally of dysuria.

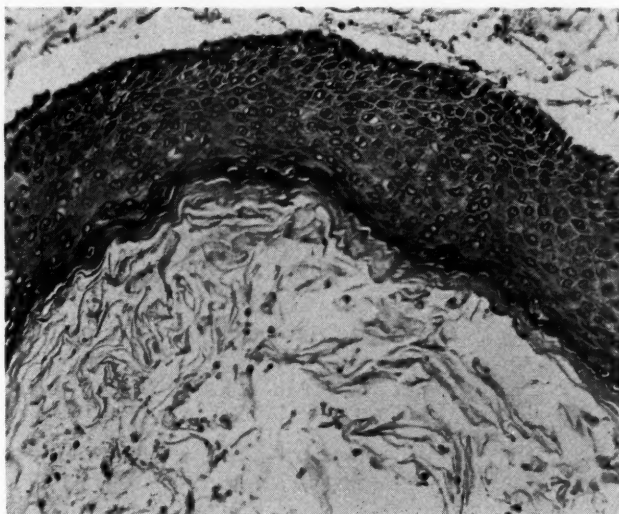


Fig. 8.—P. N., Mt.S.H.21008. Endometrial curettings. Cholesteometra. Exfoliation of lamellated masses of cornified epithelial cells and cell debris (lower segment). Note the prosoplastic epidermoid differentiation of epithelium.

On June 30, 1941 (five years after the previous admission for a curettage and radium), the patient complained of being nervous, of having gained 5 pounds in weight, and of joint pains.

At this time, examination of the uterus, which after the application of radium was reduced to normal size, revealed it to be enlarged to the size of a ten weeks' pregnancy, anterior, and softer than normal. A presumptive diagnosis of cervical stenosis with pyometra and possible fundal carcinoma was made and the patient was advised to enter Mt. Sinai Hospital on July 2, 1941.

There a curettage was done. The uterus measured about 5 inches in length by sound, was soft in consistency, and in anterior location. After dilatation of cervix 8 ounces of sebumlike material containing cholesterol crystals were evacuated from the cavity of the uterus. The uterus was then curetted. A piece of rubber tubing was inserted and anchored at the cervix, where it was allowed to remain for seven days before being removed. The patient made an uneventful recovery and was discharged from the hospital in ten days.

Microscopic examination of curettings (P. N. 21008): Large sheaths of hornifying stratified squamous epithelium apparently replacing the entire endometrium. In spite of the large amount of the material received, ordinary endometrial tissue was not found (Fig. 8).

The patient returned to Mt. Sinai Hospital on Oct. 15, 1941, where, under spinal anesthesia, a vaginal hysterectomy with anterior and posterior colporrhaphy were performed.

At this time the uterus was decreased to a size of four weeks' pregnancy only. It contained several small myomas. There was a moderate cystocele.

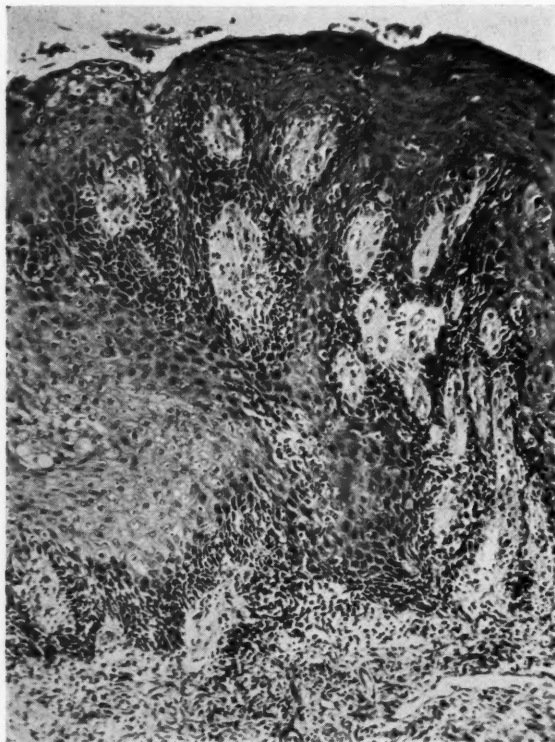


Fig. 9.—P. N., Mt.S.H.21631. Section of uterus. The entire endometrium (glands and stroma) is replaced by cornified squamous epithelium. Round-cell infiltration below the epithelium.

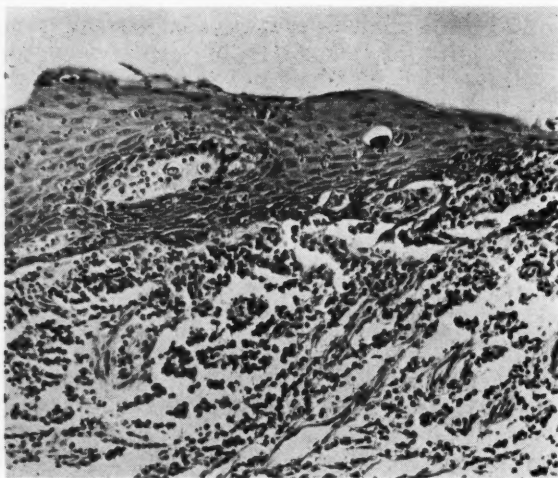


Fig. 10.—P. N., Mt.S.H.21631. Section of uterus. Epidermoid heteroplasia of endometrium. Incomplete cornification.

Pathological record of the removed uterus: (P. N. 21631).

Microscopic examination: The entire endometrium (stroma and glands) was replaced by stratified squamous epithelium. Although a careful search was made by making several sections from different parts of the uterus, the histological examination did not reveal any

evidence of endometrial glands. The stratified squamous epithelium, just as the large strips of the epithelium which were obtained at the preceding curettage, revealed all structural details of epidermis with a more or less thorough reproduction of individual layers.

It showed in many instances marked hypertrophy of the stratum corneum with a distinct parakeratotic change, alternating with areas of a frank hyperkeratosis, marked by a prominent development of stratum granulosum (Figs. 9, 10, 11).

In many parts, the epithelial covering was missing (removed at preceding curettage) and the endometrial aspect of the myometrium was converted into granulation tissue. The sections of the cervix showed that the process of epidermoid heteroplasia did not extend upon the mucous membrane of the cervical canal, which was lined by columnar epithelium.

Several myomas were found in the myometrium.



Fig. 11.—P. N., Mt.S.H.21631. Section of uterus. Papillary hypertrophy of cornified stratified squamous epithelium. Abortive cornification (parakeratosis) of stratified squamous epithelium replacing the endometrium.

Diagnosis: Cholesteometa; chronic endometritis with epidermoid heteroplasia (epidermization) of endometrium; myomatous uterus.

The patient, when last seen for a routine check-up on June 19, 1947, was apparently in excellent general health. She had gained four pounds in weight (present weight, 146 pounds). The vaginal vault was high. There was no protrusion of the vaginal walls on straining, nor was there any mass palpable in either parametrial or adnexal regions. At the time of writing this patient was in good health.

Review of Literature

Observations of stratified squamous epithelium replacing the mucosal lining of the entire cavity of the corpus uteri are rare, particularly if we exclude the cases of a frank squamous-cell carcinoma of the corpus.

Such reports have been made in connection with regenerative process in the endometrium, for instance, after curettage. Werth⁷ described a case where, ten days after a curettage, almost the entire cavity of the corpus was found to be lined by stratified epithelium in which some cells and nuclei were abnormally large, forming large epithelial buds or bands with frequent cell bridges (spinal cells?).

In this case it is not entirely clear whether the epithelium was a true stratified squamous epithelium or a stratified columnar epithelium.

Von Rosthorn⁸ reported a case, where postabortal, several-times-repeated curettage, and caustics used for treatment of so-called "interstitial endometritis" led to the removal of the uterus. The cavity of the latter was lined by stratified squamous epithelium which was cornified.

There are numerous reports of stratified squamous epithelium replacing the endometrium in connection with a chronic suppurative process in the cavity of the uterus (pyometra),⁹ nonspecific and specific, as tuberculosis,¹⁰ or syphilis.¹¹

Rather important for the histogenetic interpretation are the occasional findings of stratified squamous epithelium in the cavity of the corpus uteri without any apparent cause, as for instance of old women.¹²

Such localized or general replacement of the endometrium by stratified squamous epithelium without any apparent cause was explained by Meyer as an act of prosoplasia of epithelium, which resulted from the loss of its normal functional activity because of the senile state of the organ (uterus).¹³

The cases reported in the literature do not make it clear whether the epithelium found in the uterus was a true stratified squamous epithelium or only a columnar epithelium forming several rows of cells (stratified columnar epithelium). Several observations mention only stratification of large polyhedral cells (flattened cells). In many cases cornification and the differentiation to spinal cells was reported lacking, or abortive only. Only sometimes a basal layer or a stratum corneum were mentioned.

For instance, Sitzenfrey, in a case of tuberculosis of the uterus, reported that in some areas not only the surface epithelium, but also the glandular epithelium formed several rows. The individual cells were large and polyhedral. However, he stated frankly that the typical arrangement of stratified squamous epithelium was lacking, to such an extent that the atypical appearance of stratified squamous epithelium in his cases made the differentiation between malignant and benign process rather difficult.

E. Kaufman (*Lehrbuch d. spez. path. Anat.*, III Aufl., 1904) described a case of "cholesteatoma" of the uterus, which is in many ways similar to our case. He stated that the distended cavity was filled with cholesterol crystals and desquamated epithelial cells. The mucous membrane was atrophic and was converted into stratified squamous epithelium.

Of paramount importance for the conception of the origin of stratified squamous epithelium are observations obtained in uteri of children and newborn infants.¹⁴

Meyer¹⁵ reported, for instance, islands of stratified squamous epithelium in the endometrium of the lower part of the uterus of a newborn.

Hohl¹⁶ reported islands of stratified squamous epithelium between the upper and middle third in the cavity of the uterus of three children.

For the pathogenesis of formation of stratified squamous epithelium in the endometrium is of certain interest an observation reported by Zondek,¹⁷ who described among other effects of large doses of follicular hormone upon the uterus of the rat partial or total conversion of surface epithelium into stratified cornified epithelium, changing the gross appearance and the histological picture of the endometrium to that of vaginal epithelium in the state of estrus.

He observed also as the result of prolonged treatment with follicular hormone (in twelve rabbits) the association of the conversion of endometrium into stratified squamous epithelium with inflammatory changes in the uterus, resulting in suppurative destruction of the endometrium and even the myometrium.

The cultures made from the suppurative material gave negative findings (sterile). The necrosis of tissue was considered primarily as aseptic. The ovaries were found to be atrophic in these experiments.

Summary

The case reported in this paper represents a gradual progressive replacement of surface epithelium, and the epithelial lining of the glands of the endometrium, by stratified squamous epithelium with ultimate loss of all typical histological constituents of the endometrium, the stroma and the epithelium.

The process of epidermoid heteroplasia of endometrium, which we think is a proper name for the heteroplastic differentiation of basal epithelial cells of the surface epithelium and epithelial lining of the glands of the endometrium, was observed by us through a period of five years.

It was finally complicated by cholesteometra, which we believe is a more proper designation for the distention of the cavity of the uterus by lamellated strips of cornified epithelial cells and sebum-like material than cholesteatoma (Kaufman).

While it is possible that in the final phase of the process of epidermoid heteroplasia (epidermization) of the endometrium of the corpus uteri, the inflammation could be an important contributory factor, we are by no means certain about the actual course of events. Whether the inflammation destroys the endometrium and, in the process of ensuing regeneration, the forces which were harbored in the basal cells of the endometrium find an outlet leading to heteroplastic development of the epithelium, or whether the inflammation itself, after the destruction of the normal endometrium, actually stimulates the development of stratified squamous epithelium from basal cells, we could not decide with certainty.

The experiment of Zondek, mentioned in the discussion of literature, permits as assumption that certain agents, even if primarily of a specific trophic nature, as estrogens are in case of endometrium, may lead, if applied in unusually large doses, to actual destruction of the target tissue.

Because of the environmental change produced by the administration of massive doses of the above-mentioned agent, and the destruction of the original tissue, the normal constituents of the latter are inhibited in their regenerative properties, and the regeneration of tissue follows heterologous patterns resulting, as for instance in our case, in formation of stratified squamous epithelium instead of the ordinary columnar epithelium.

The process of replacement of the columnar epithelium of the endometrium (surface epithelium and epithelial lining of the glands) by stratified squamous epithelium as observed in our case follows in general the morphologic patterns which were established by Meyer for the process of epidermization of cervical erosion.

This process of replacement of one type of epithelium by another does not have to be identified with process of metaplasia.

The development of stratified squamous epithelium in lieu of the endometrium (glands and stroma) in our case, presents only another example of heteroplastic differentiation of the basal cells of this region.

The associated heteroplastic differentiation of stroma we consider as particularly essential for the above-mentioned heterologous differentiation of the epithelium.

The abandoning of the concept of metaplasia and the acceptance instead of the concept of heterologous differentiation of the basal cells of the uterine epithelium (surface epithelium and the epithelial lining of the endometrial glands) has a purpose of immeasurable diagnostic significance because it lifts the mystery which has always enveloped the process of metaplasia and substitutes the latter with a rational step-by-step descriptive explanation of histological events.

The exact understanding of the process brought by descriptive explanation reduces the possibilities of diagnostic deception which could take place in the interpretation of confusing epithelial patterns arising in the process of heterologous differentiation of basal cells of the uterine epithelium.

The process of epidermoid differentiation of basal cells of uterine epithelium is gradual.

Because it goes through the stage of initial incomplete differentiation, which is deceptively similar to the state of inadequate differentiation of epithelium (anaplasia), usually associated with clinical malignancy, it could be easily mistaken for an early carcinoma (carcinoma in situ).

Therefore, particularly, the exact understanding of the process of epidermoid heteroplasia of basal cells and the exact knowledge of all resulting and associated complicated epithelial pattern are essential to avoid such diagnostic error.

The case reported in this paper illustrates different phases of the process of epidermoid heteroplasia of basal cells of uterine epithelium, including the initial stage of incomplete differentiation of stratified epithelium, which could have been easily mistaken for beginning carcinoma.

The prosoplastic (beyond the normal) differentiation of stratified squamous epithelium, which was observed at the end of the process (five years after the initial observation), may serve as another evidence that the anaplastic appearance recorded in the initial observation was only a transitory phase of differentiation of epithelium (which went beyond the normal mark), and not a beginning of a state of progressive anaplasia, associated with carcinoma.

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SARCOMA OF THE UTERUS

A Review of Thirty-Three Cases

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SARCOMA of the uterus is sufficiently rare that the experience of individual hospitals deserves recording. Thirty-three sarcomas of the uterus were treated at the Woman's Clinic of the New York Hospital from 1933 to 1949. Since there were 22,539 admissions to the gynecological service, the incidence was 1:683 or 0.15 per cent of all admissions. Approximately 1,000 women were treated for cancer of the genital tract during this period; therefore, sarcoma constituted 3.3 per cent of all genital-tract neoplasms, and the ratio of sarcoma to carcinoma is 1:30. The type of sarcoma is shown in Table I. There was insufficient pathological evidence in the 2 unclassified sarcomas to determine whether origin was endometrium, myometrium, or some other connective-tissue source. Since approximately 5,430 myomas were observed during this period, 16, or 1:300 or 0.3 per cent, showed leiomyosarcoma. Thirty of these patients received their initial treatment at the Woman's Clinic. Three patients, all of whom had leiomyosarcoma, had been treated elsewhere prior to their admission with recurrent sarcoma.

The ages ranged from 28 to 81 years; the mean was 56 years. There were no sarcomas in children. The age distribution was as follows:

20 to 29 years	1
30 to 39 years	1
40 to 49 years	7
50 to 59 years	10
60 to 69 years	10
70 to 79 years	3
80 to 89 years	1

Regardless of the type of sarcoma, 31, or 93 per cent, of the patients were over 40 years of age.

The marital status and parity were as follows: Four patients were single; ten of the twenty-nine who were married were nulliparas; two had borne one child; seven had borne two children; and ten had borne three or more children.

Four patients had received radium previously; one with endometrial sarcoma for irregular bleeding eleven years ago; a second, with sarcoma arising in a myoma, had been treated by radium for myomas six years previously; a third with myometrial sarcoma had received radium for irregular bleeding 10 years ago; while the last patient with unclassified sarcoma had been treated by radium one year ago for carcinoma of the endometrium. Since the last patient undoubtedly had sarcoma at the time of the radium insertion, radium was inserted in three, or 8.3 per cent, of the patients prior to the development of sarcoma.

TABLE I. CLASSIFICATION OF SARCOMA OF THE UTERUS

TYPE	NUMBER
1. Endometrial sarcoma	13
2. Myogenic sarcoma	18
a. Myoma	16
b. Myometrium	2
3. Unclassified sarcoma	2
Total	33

Postmenopausal bleeding, abdominal pain, and the development of an abdominal mass were the leading symptoms as outlined in Table II. Twelve patients were still menstruating. Eleven of the twenty-one patients who had ceased to menstruate developed postmenopausal bleeding. Almost all, six of the seven postmenopausal patients with endometrial sarcoma bled, while only three of the nine patients with leiomyosarcoma, who were past the menopause, bled; and both of the patients with unclassified sarcoma showed postmenopausal bleeding. Bleeding in patients with leiomyosarcoma occurred only when there was direct invasion and ulceration of the overlying endometrium. Four patients with endometrial sarcoma and three patients with leiomyosarcoma showed rapid increase in the size of the uterus. Two of the three patients with leiomyosarcoma were four and six years past the menopause. The short duration of symptoms is well exemplified in Table III. Nineteen, or 60 per cent, of these patients had symptoms of less than 6 months' duration, while only 6, or 20 per cent, had symptoms for more than a year.

TABLE II. SYMPTOMS OF SARCOMA OF THE UTERUS

SYMPTOMS	TYPE			TOTAL
	ENDOMETRIAL	MYOMETRIAL	UNCLASSIFIED	
Postmenopausal bleeding	6	3	2	11
Pain	4	6	1	11
Abdominal mass	1	6	2	9
Abdominal enlargement	3	3	1	7
Irregular bleeding	2	2		4
Discharge	2	1		3
Weight loss		3		3
Intestinal obstruction		1		1
Edema		1		1
Weakness		1		1

TABLE III. DURATION OF SYMPTOMS

MONTHS	TYPE			TOTAL
	ENDOMETRIAL	MYOMETRIAL	UNCLASSIFIED	
Less than 1	1	2		3
1-3	2	5		7
3-6	4	3	2	9
6-9	2			2
9-12	2	4		6
12-24	2	3		5
24+		1		1
Total	13	18	2	33

The chief physical sign was enlargement of the uterus. All but one of these patients had an enlarged uterus (Table IV). This enlargement was due to the sarcoma itself in half of the cases and was due to associated myomas in the other half. One sarcoma degenerated to form a uterine cyst which contained six liters of blood, fluid, debris, and sarcoma.

Three patients had ascites. This sign did not appear until invasion through the serosa of the uterus had occurred. Its presence indicated sarcoma which has invaded the peritoneum and which, regardless of its grade of histological malignancy, had extended to such a degree that it was inoperable.

TABLE IV. SIZE OF UTERUS

SIZE	TYPE			TOTAL
	ENDOMETRIAL	MYOMETRIAL	UNCLASSIFIED	
Normal	1			1
Less than halfway to umbilicus	2	2	2	6
Halfway to umbilicus	7	6		13
Above umbilicus	3	10		13
Total	13	18	2	33

Cytological smears were obtained from nine patients (25 per cent) as shown in Table V. Since only exfoliative lesions can be detected by this technique, it is not surprising that all of the endometrial sarcomas were diagnosed correctly and that the two false negative reports occurred in myogenic sarcoma. The malignant cells resembled their prototypes in histological sections and hence were easy to recognize. If vaginal smears only had been taken in three patients with cervical stenosis, the false negative reports would have lulled the physician into an unwarranted sense of security.

TABLE V. CYTOLOGICAL SMEARS

TYPE	YEAR	SOURCE	REPORT	ACCURACY
Endometrial	1944	Vagina	Positive	Yes
Endometrial	1944	Vagina	Positive	Yes
Endometrial	1947	Vagina	Positive	Yes
Leiomyosarcoma	1933	Vagina	Positive	Yes
Leiomyosarcoma	1946	Vagina	Negative	Error
Leiomyosarcoma	1948	Vagina	Doubtful	Error
Leiomyosarcoma	1948	Vagina	Positive	Yes
Unclassified	1934	Vagina	Positive	Yes
Unclassified	1948	Vagina and Cervix	Positive	Yes

TABLE VI. OPERATIVE TREATMENT

OPERATIONS	TYPE			TOTAL
	ENDOMETRIAL	MYOMETRIAL	UNCLASSIFIED	
<i>Minor.—</i>				
Curettage	7	2		9
Cervical biopsy	4			4
Vaginal biopsy	2	1		3
Paracentesis		1		1
Colpotomy		1		1
				<hr/> 18
<i>Major.—</i>				
Myomectomy		1		1
Exploratory laparotomy and biopsy		1	1	2
Subtotal hysterectomy	3	9	1	13
Total hysterectomy	8	5		13
Bowel resection		1		1
				<hr/> 30
Total				<hr/> 48

Table VI shows the surgical treatment of sarcoma. Total hysterectomy was performed in 13, or 40 per cent. An additional 13 patients who were treated by

subtotal hysterectomy either had too extensive lesions to permit total hysterectomy, or the presence of sarcoma was not recognized at the time of operation. Since 90 per cent of all hysterectomies now performed at the Woman's Clinic are of the total type, there will be fewer incomplete hysterectomies in patients with unsuspected sarcoma. Finn and Muller⁴ in a recent review of myomectomy found only one leiomyosarcoma in approximately 250 patients with myomectomy. This fact, plus the rarity of sarcoma in women under 40 years of age attests to the safety of myomectomy. Total hysterectomy and bilateral salpingo-oophorectomy were performed after myomectomy had revealed a leiomyosarcoma with invasion of the capsule in a 28-year-old married nulliparous woman.

Surgeons have hesitated to operate on patients with uterine sarcoma because of the high immediate postoperative mortality rate. Three of the thirty patients who had major operations and two of twenty-eight patients who had minor operations died during the immediate postoperative period as shown in Table VII. These five deaths after forty-eight operations constitute an incidence of 10 per cent. Death in three patients with advanced sarcoma was due to hemorrhagic shock. The uterine vessels could not be identified in one patient, autopsies on the other two revealed hemoperitoneum.

TABLE VII. IMMEDIATE POSTOPERATIVE DEATHS

TYPE	OPERATION	DAY	CAUSE
		POSTOPERATIVE	
Endometrial	Total hysterectomy	1	Hemorrhagic shock
Leiomyosarcoma	Exploratory laparotomy and biopsy	1	Congestive heart failure
Leiomyosarcoma	Exploratory laparotomy and biopsy	2	Hemorrhage and peritonitis
Leiomyosarcoma	Colpotomy	8	Hemorrhagic shock
Endometrial	Curettage	11	Peritonitis

X-ray irradiation was administered to only seven patients; five with endometrial sarcoma, one with leiomyosarcoma, and one with unclassified sarcoma. Only two of these patients are still alive. The sarcoma in both of these instances was confined to the endometrium, indicative of a favorable prognosis regardless of irradiation. The five patients who died had extensive sarcomatosis and, hence, the irradiation was probably futile.

TABLE VIII. CAUSE OF DEATH

CAUSE	TYPE			TOTAL
	ENDOMETRIAL	LEIOMYOSARCOMA	UNCLASSIFIED	
Metastases	3	7	2	12
Shock	1	1		2
Uremia	1	1		2
Peritonitis	1	1		2
Cardiac		1		1
Total				19

Nineteen of these patients have died as outlined in Table VIII: six had endometrial sarcoma, eleven had leiomyosarcoma, and two had unclassified sarcoma. Seven patients have survived for less than five years: two had endometrial sarcoma and five had myogenic sarcoma. One of the latter has pulmonary metastases three years after operation. Seven patients (21 per cent) have survived longer than the conventional five-year period. Five with endometrial sarcoma have survived from six to seventeen years; two with leiomyosarcoma

have survived eight and one-half and sixteen years, respectively. Survival in relation to the type of sarcoma is shown in Table IX. Survival was charted against the anatomical extent of the sarcoma. The direct correlation between the extent of the sarcoma and survival is depicted graphically in Table X. There is a similar direct correlation between the completeness of the operation and survival. No patient in whom only exploratory laparotomy or minor diagnostic studies were performed survived for five years. Seven of the twenty-six patients who were treated by hysterectomy have survived for five or more years, as shown in Table XI.

TABLE IX. SURVIVAL IN RELATION TO TYPE OF SARCOMA

TYPE	TOTAL	SURVIVING MORE THAN 5 YEARS		SURVIVING LESS THAN 5 YEARS		DEAD	
		NUMBER	%	NUMBER	%	NUMBER	%
Endometrial	13	5	39	2	15	6	46
Myometrial	18	2	11	5	27	11	62
Unclassified	2	0	0	0	0	2	100
Total	33	7	21	7	21	19	58

TABLE X. SURVIVAL AND ANATOMICAL EXTENT

EXTENT	TOTAL	SURVIVING MORE THAN 5 YEARS		SURVIVING LESS THAN 5 YEARS		DEAD	
		NUMBER	%	NUMBER	%	NUMBER	%
1. Confined to the endometrium or within capsule of the myoma	11	5	45	4*	37	2	19
2. Penetration of subendometrial myometrium or capsule	4	1	25	1	25	2	50
3. Involvement of deep myometrium	4	1	25	1	25	2	50
4. Involvement of serosa, pelvic organs, or pelvic lymph nodes	8	0	0	0	0	8	100
5. Extrapelvic involvement	6	0	0	1	17	5	83

*One patient surviving 3 years with lung metastases.

The fact that metastases were the leading cause of death, regardless of the type of sarcoma, indicates the rapidity of extension and the high incidence of recurrence. The following sites of metastases were observed by physical examination, x-ray, laparotomy, pathological examination of the surgical specimen, and, in seven instances, by post-mortem examination.

Pelvic organs	9
Lungs	8
Vagina	7
Extra-pelvic lymph nodes	3
Bowel	3
Ovary	3
Omentum	2
Ureter	2
Cervix	1
Skin	1
Diaphragm	1
Spleen	1
Bone	1

Sarcoma spreads by direct extension as well as by vascular and lymphatic dissemination. Autopsies were performed on seven patients, 35 per cent of those who died. Three patients had endometrial sarcoma and four had myogenic sarcoma.

TABLE XI. SURVIVAL AND COMPLETENESS OF OPERATION

OPERATION	TOTAL	SURVIVING 5 YEARS		SURVIVING LESS THAN 5 YEARS		DEAD	
		NUMBER	%	NUMBER	%	NUMBER	%
Total hysterectomy	13	3	23	3	23	7	54
Subtotal hysterectomy	13	4	30	4*	30	5	40
Exploratory laparotomy and biopsy	2	0	0	0	0	2	100
Minor operation	5	0	0	0	0	5	100

*One alive 3 years with lung metastases.

Comment

The difficulties of pathological diagnosis result in false positive and false negative diagnoses of sarcoma. The initial pathological diagnosis of curettings or cervical biopsies was considered to be sarcoma in sixteen patients, as shown in Table XII; eight of these were shown by further investigation to have carcinoma, while exhaustive study in the remaining eight patients failed to reveal any malignant disease. The inclusion of such patients leads to fallacious conclusions and artificially improves the survival rate. Such false positive diagnoses have been excluded by rigid re-examination of all slides. Three patients with carcinosarcoma or mixed mesodermal tumors and two patients with malignant lymphomas have also been excluded. Slides of all five-year survivors have been reviewed by other pathologists and accepted as sarcoma.

The false negative diagnoses are the more important because of the delay in effective treatment. There were six such diagnoses (Table XII). The original diagnosis in three of these patients was degenerated decidua. This delayed treatment for two years and nine months in one patient with endometrial sarcoma. Three years after the correct diagnosis was established and hysterectomy performed, lung metastases appeared. The treatment in another patient with endometrial sarcoma was delayed for two months; death from widespread metastases occurred six months after hysterectomy. The erroneous diagnosis of degenerated decidua delayed hysterectomy for two months in a third patient with endometrial sarcoma without apparent ill effect. Two other patients, in whom the original diagnosis was benign cellular myoma, subsequently developed metastases of leiomyosarcoma. The first patient developed pulmonary metastases. A review of the slides revealed leiomyosarcoma. The second patient developed metastases to the lumbar vertebrae and sacrum from leiomyosarcoma two and one-half years after total hysterectomy for myomas; review of these slides showed only myomas with hyaline degeneration, but slides had not been prepared from all of the myomas and the specimen had been discarded at the time of the review. Two similar patients were admitted from other hospitals after subtotal hysterectomies for supposedly benign cellular myomas. Review of these slides revealed leiomyosarcoma in each instance. The diagnosis of endometrial carcinoma which was made in the sixth case, while incorrect, did not delay definitive treatment, at which time the correct diagnosis of endometrial sarcoma was made.

Sarcoma in this series represented 3.3 per cent of all of the malignancies of the female genital tract. This coincides with the 3.1 per cent incidence reported by Novak and Anderson⁹ and the 3.2 per cent incidence of Kimbrough.⁸ Myomas showed a 0.3 per cent incidence of sarcoma. The extremes range from 0.2 per cent reported by Randall¹² to the 6.0 per cent of Proper and Simpson.¹¹ The average is closer to the 0.56 per cent of Novak and Anderson,⁹ the 0.76 per cent of Kimbrough⁸ and the 1.0 per cent of Bosse and Stanton¹ and of Handley and Hawkins.⁶

Sarcoma affects middle-aged women despite the repeated allegations that it is a disease of only the extremes of life. The leading symptom is postmeno-

pausal bleeding, once more bolstering the axiom that recurrence of bleeding after the menopause indicates the presence of malignant disease till it is disproved. Symptoms were of short duration. They were of less than six months' duration in more than half of the patients and were of more than two years' duration in only one patient. Errors in correct diagnosis, as discussed above, led to delays in proper treatment.

TABLE XII. ANALYSIS OF TRUE DIAGNOSES

<i>True Diagnosis in False Positive Diagnosis of Sarcoma.—</i>		
Carcinoma		8
Endometrium	4	
Cervix	4	
Benign Lesions		8
Cellular myomas	5	
Chronic endometritis	2	
Degenerated decidua	1	
		<hr/> 16
<i>Original False Negative Diagnosis When True Diagnosis Was Sarcoma.—</i>		
Degenerated decidua		3
Cellular myoma		2
Endometrial carcinoma		1

Cytological smears were of value in diagnosis and were correct in seven out of nine instances. Both errors in cytological diagnosis occurred in leiomyosarcomas which arose in myomas and which probably did not shed cells into the endometrial cavity. It is of interest that two such sarcomas exfoliated sufficiently to be recognized by cytological methods.

The treatment of myomas has progressed a long way since thirty-five years ago, when the efficacy of the surgical treatment of myomas was still disputed. Fullerton⁵ and others at that time thought that the 4 per cent mortality from hysterectomy was higher than the expected 2 per cent incidence of sarcoma. Some authors, including Proper and Simpson,¹¹ went to the opposite extreme and recommended immediate surgical removal of all myomas. In general, we remove only symptomatic myomas, but recommend hysterectomy sooner if clinical suspicion of sarcoma develops. Such suspicions as outlined by Dalton² are: bleeding or growth of myoma after the menopause, rapid growth of the myoma, ascites, cachexia, or general symptoms. These are very late signs and surgery should be done prior to the development of the last three. Seitz and Wintz¹⁴ at the German Gynecological Congress of 1920 concluded that since the results of irradiation for sarcoma were so satisfactory no patient need undergo operation. Perry¹⁰ recently reported that radium was of benefit in two patients. Most others authors, including Smith,¹⁵ doubt the efficacy of irradiation therapy. The value of irradiation is difficult to assess in this series. Its postoperative use in two patients with sarcoma confined to the uterus was probably unnecessary, while the death after irradiation of five patients with advanced sarcoma would indicate that it is of questionable value.

Three patients (8.3 per cent) had been treated by radium for benign lesions such as myoma or irregular bleeding 6, 10, and 11 years prior to the development of the sarcoma. The sarcomagenic effect of radium has not been proved in human beings, although several recent authors suggest that radium has a sarcomagenic effect. Scheffey¹³ denies such an effect, stating, "Errors in omission, either in technique or judgment as commented upon, and not the radiation therapy itself, were the responsible factors in the subsequent occurrence of malignancy."

Complete extirpative surgery appears to be the best treatment. The incidence of postoperative death was 10 per cent. This was due to hemorrhagic

shock and peritonitis and usually occurred in far-advanced sarcomas with hopeless prognosis. Hence, sarcoma should not connote inoperability as it does to so many surgeons.

Prognosis has been based by Evans,³ Handley and Hawkins,⁶ and Kimbrough⁸ upon the number of mitotic figures. This, while a valuable index, is time consuming and if the anatomical extent of the sarcoma is not considered, is misleading. A patient with a sarcoma of the highest grade of malignancy and with numerous mitotic figures has a good prognosis if the sarcoma has so stayed within the confines of the uterus that it can be removed completely by surgery. Bosse and Stanton¹ showed the dependence of prognosis and survival upon invasiveness inasmuch as 12 of their 14 patients without invasion were alive and well, while all 13 with invasion died or showed recurrence. Only one of our 14 patients with spread outside of the uterus is alive.

Randall¹² reported that 6 of 8 patients (75 per cent) with myogenic sarcoma survived for 5 years, while only 3 of 21 (14 per cent) others, including cases of endometrial sarcoma, survived. Endometrial sarcoma in this series and contrary to most reports had by far the best survival rate of all the types of sarcoma. Five (39 per cent) of the patients with endometrial sarcoma were alive without recurrence 5 years after treatment, while only 2 (11 per cent) of the patients with leiomyosarcomas were alive after 5 years. This favorable prognosis in endometrial sarcoma was due to the early appearance of symptoms, notably postmenopausal bleeding. The poor survival in leiomyosarcoma is due in part to the rigid exclusion of all benign cellular myomas. Three of the patients with leiomyosarcoma had been treated elsewhere by subtotal hysterectomy and when first seen here had far-advanced sarcoma.

No sarcomas of the ovary, tube, cervix, or vagina were observed during this study. One melanosarcoma of the vulva was treated. No instances of the so-called "stromatosis" occurred.

The autopsies provided additional pathological knowledge of extension and recurrence. The most common sites of metastases were the pelvic organs, the lungs, and the vagina. Smith¹⁵ found metastatic sarcoma of the lungs in 5 of 24 patients with sarcoma of the uterus.

There is a growing tendency to determine the malignancy of the tumor by the survival of the patient. This viewpoint is held by Bosse and Stanton¹ in regard to sarcoma. However, we believe that gross and microscopic examination determine the malignancy of sarcoma, while survival indicates the thoroughness of the surgical extirpation. It has been stated that no patient with sarcoma of the uterus has survived for 5 years. Healy⁷ in the discussion of Novak and Anderson's⁹ report stated that only 2 of 23 patients at the Memorial Hospital were alive and that both of these had pulmonary metastases. This hopeless prognosis is contrary to our experience, since 7 patients (21 per cent) have survived for more than 5 years. Three of these patients are alive more than 10 years after operation. The consensus of the five-year survival recorded in the literature is about 25 to 30 per cent.

Summary

Sarcoma of the uterus comprised 0.15 per cent of all admissions to the Woman's Clinic of the New York Hospital from 1933 to 1949. It represented 3.3 per cent of all genital-tract neoplasms, and 0.3 per cent of myomas were leiomyosarcomas. There were 13 endometrial, 18 myogenic, and 2 unclassified sarcomas. Thirty-one (93 per cent) of the patients were over 40 years of age. The chief symptoms were postmenopausal bleeding, abdominal pain, and the appearance of an abdominal mass. The uterus was enlarged in all but one

patient. Radium had been previously inserted for benign causes in 3 (8.3 per cent). Cytological smears were obtained from 9 patients. Seven were correct (5 endometrial and 2 myogenic sarcomas) while the 2 false negative reports occurred in leiomyosarcoma.

Surgery is the treatment of choice. The immediate postoperative mortality was 10 per cent. X-ray irradiation was not effective in 5 patients with advanced sarcoma. Regardless of the histological grade of sarcoma and the number of mitotic figures, the anatomical extent of the sarcoma is the most important factor in prognosis. Only one patient is alive in whom the sarcoma had extended outside of the uterus, while 13 patients in whom the sarcoma was confined to the uterus are alive. Nineteen patients have died; 6 had endometrial, 11 had myometrial, and 2 had unclassified sarcoma. Autopsies which were performed on 7 patients showed that metastases were the leading cause of death. Fourteen patients are alive. Seven, 2 with endometrial sarcoma and 5 with myometrial sarcoma, have lived for less than 5 years. Seven patients (21 per cent) have survived from 5 to 17 years. Five of these patients had endometrial sarcoma, while 2 had leiomyosarcoma.

The author wishes to express his gratitude to Dr. R. Gordon Douglas for his permission to publish these cases and for his painstaking correction of the manuscript, and to Drs. Carl T. Javert and John Pearce for checking the slides of the patients who have survived for more than 5 years.

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ECLAMPTIC MANIFESTATIONS OCCURRING IN PREGNANCY COMPLICATED BY BRAIN TUMOR

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BRAIN tumor is a comparatively rare complication of pregnancy. The standard textbooks of obstetrics and neurology mention the subject briefly or not at all. This was emphasized recently by Rand and Andler,¹ neurosurgeons, who reported six proved and three probable cases of brain tumor in pregnancy. On reviewing the literature, they found scattered case reports, many of them in the older German literature, but a comprehensive modern survey was lacking. Bickenbach² in 1929 stated that only about 25 cases had been reported, and although no complete count has been made, it appears from the report of Rand and Andler¹ that less than 50 cases are on record. It is probable that the frequency of the combination is greater than these figures would indicate.

All authors, whether obstetricians or neurosurgeons, have agreed that the clinical picture of eclampsia may closely resemble that of brain tumor in pregnancy, and vice versa. Bernard³ in 1898, stated that convulsions and increasing hypertension may be found either in eclampsia or in brain tumor during pregnancy. He commented on the difficulty in diagnosis when convulsions and coma occur during pregnancy. Alpers and Palmer⁴ report in detail a case in which a diagnosis of brain tumor in pregnancy was entertained because of papilledema, progressive vomiting, and progressive lethargy. Autopsy showed only punctate hemorrhages in the brain, and the case was felt to be one of toxemia of pregnancy. In a discussion of "Cerebral and Spinal Complications of Pregnancy" they state that brain tumor is a rare complication. A number of reported cases have been treated as eclampsia until death, and the diagnosis of brain tumor made at autopsy.^{5, 6, 7} Moreover, several instances are on record in which brain tumors have been strongly suspected during more than one pregnancy, and have produced symptoms only during the last trimester. Dexter and Weiss⁸ report a remarkable case in which numbness of the foot, weakness, loss of memory, speech difficulty, and finally hemiparesis occurred, with rapid recovery following delivery. A similar syndrome appeared during the patient's next pregnancy three years later, with marked regression following delivery. Postpartum studies resulted in a diagnosis of brain tumor and at operation a glioma involving the frontal and parietal regions of the left hemisphere was found.

Many authors have noted that pregnancy may have an adverse effect on the growth and symptomatology of brain tumors. Cushing,⁹ in reporting a case of cystic hemangioma, stated, "Pregnancy, however, appears to be a not uncommon provocative element in bringing tumors to light, more particularly, perhaps, angiomatous lesions." Rand and Andler¹ feel that there is greater cerebral edema surrounding a glioma than a benign tumor, and note that "the pregnant state probably tends even more to increase this edema."

In view of this similarity in clinical manifestations, it is surprising to note that among the numerous comprehensive reviews and reports on the pathological findings in eclampsia, no case has been reported in which brain tumor was found, and in which the visceral organs showed the changes formerly described as characteristic if not diagnostic of eclampsia. Way¹⁰ mentions arteritis, necrosis, and hemorrhage as brain lesions in 33 cases of fatal eclampsia. Acosta-Sison¹¹ examined the brain in 16 cases of eclampsia and found edema, congestion, and hemorrhage, but in 7 cases the brain was thought to be normal. The work of Dexter and Weiss⁸ includes a review of the pathological findings in 25 fatal cases, and brain tumor is not mentioned. Stander¹² and Dieckmann,¹³ in longer reviews of the entire subject of toxemia of pregnancy, make no reference to this combination. It seems unlikely that the finding of a brain tumor, however small, would have been ignored in these eclamptic patients, most of whom suffered convulsions.

The present report describes a patient, estimated to be in the twenty-fourth week of gestation, who entered the hospital following sudden and almost simultaneous onset of hypertension, convulsions, albuminuria, and edema. The clinical picture was that of eclampsia.

Mrs. K. B., aged 28 years, white, gravida ii, para 0, was admitted to the Obstetrical Service at Bellevue Hospital on July 16, 1949, at 2:15 A.M. with a history of severe frontal and parietal headaches which had begun acutely at 10 P.M. of the preceding day. At midnight she had a convulsive seizure from which she recovered consciousness followed by a second, at 1:00 A.M. following which she remained in coma. A third seizure occurred while en route to the hospital. These seizures were characterized by tonic and clonic contractions, champing movements of the jaw, tongue biting, and foaming at the mouth. She was in about the twenty-fourth week of her second pregnancy, the first being terminated by spontaneous early abortion in 1948.

Her history was obtained from her family, the remote details being irrelevant. She had been noted to be mentally on edge during the past four months and on one occasion had fainted. There was no history of previous convulsions. Her pregnancy had proceeded in a normal fashion and she had registered at the antepartum clinic of a neighboring hospital. Here she had made five visits, the last, two days before the onset of her illness. The physical findings noted on these occasions were normal, the blood pressure varying between 110/70 and 130/80, the gain in weight not being excessive, and a slight trace of albumin being present in the urine on the last two occasions. The Mazzini test was negative.

Within ten minutes of admission a fourth convulsion occurred, identical to those previously described. When this had ceased, examination showed a young woman in deep coma with rapid labored respirations, pulse rate of 92, and a temperature of 99° F. Abdominal examination showed an intrauterine pregnancy estimated to be about 24 weeks in duration, the fetus presenting as a vertex, with an audible fetal heartbeat. Both ankles showed pitting edema. The reflexes, at first found to be hypoactive, within 20 minutes were noted to be hyperactive. The blood pressure was 170/120. Examination of a catheterized specimen of urine showed a 1 plus reaction for albumin and 2 plus for acetone. She was given immediately 20 c.c. of 10 per cent magnesium sulfate, 50 c.c. of 50 per cent glucose, and 0.5 Gm. of Sodium Amytal intravenously. Within twenty minutes the blood pressure had fallen to 120/80 but the reflexes were still noted to be hyperactive. During the remainder of the night the blood pressure fluctuated between 115/80 and 150/100. A second dose of magnesium sulfate, 20 c.c., was given at 4:30 A.M. and additional Sodium Amytal, 0.25 Gm., at 5 and 6 A.M. The patient remained in coma but no additional convulsions occurred. While eclampsia was considered as the most likely diagnosis, the atypical character of the case was puzzling.

At 9 A.M. her condition was unchanged, the coma persisting, the breathing being stertorous and labored, the blood pressure and reflexes being within normal limits. She was in-

continent. Shortly after these observations, respiration ceased and deep cyanosis appeared. Artificial respiration was commenced immediately in bed. Aspiration of the nasopharynx yielded a large amount of dark brown mucus. An anesthetist was called who quickly and without difficulty inserted an intratracheal catheter and began artificial respiration through a closed system using positive oxygen pressure. These measures resulted in the disappearance of all evidence of anoxemia. The heart rate remained normal throughout. The reflexes had completely disappeared. After 30 minutes of controlled respirations, receiving 100 per cent oxygen with carbon dioxide absorption, the patient was transferred to a Drinker respirator.

A bronchoscopy was done which revealed a minimal amount of mucus in the right lobe bronchus and left main bronchus. The segmental bronchi were clear. It was the impression of the bronchoscopist that the respiratory failure was not due to obstruction. Pulse was now thready with a rate of 112. Catheterized urine yielded a volume of 170 c.c. which showed a 2 plus reaction for albumin but the microscopic examination was negative. Blood chemistry determinations showed the nonprotein nitrogen to be 39 mg. per cent, carbon dioxide combining power 20 volumes per cent. The carbon dioxide combining power was repeated and later reported as 38 volumes per cent. Lumbar puncture was done in the respirator but pressure recordings were unobtainable because of mechanical difficulties. However, the spinal fluid did not appear to be under increased pressure. Twenty c.c. of spinal fluid were withdrawn which appeared clear and showed no evidence of blood or xanthochromia. Examination of the fluid showed a negative cell count, negative Pandy test, and no increase in total protein. The glucose was reported as 20 to 30 mg. per cent. The Wassermann and Mazzini tests were reported negative.

Fluids were started intravenously and given at a slow rate of 10 to 15 drops per minute.

During the next three days in the respirator the patient's condition remained essentially unchanged. She was seen by medical, neurosurgical, and neurological consultants. Many diagnoses were entertained, including (1) intracranial hemorrhage, (2) intracerebral hematoma, (3) pontine hemorrhage, (4) poliomyelitis, (5) encephalitis, and (6) cerebral anoxia involving the respiratory center, secondary to eclamptic convulsions. At the suggestion of the neurosurgeons 0.5 Gm. of caffeine sodium benzoate was given intramuscularly every three hours and 20 mg. of benzedrine were added to each of the infusions.

Several fundoscopic examinations were done but the eyegrounds were described as normal.

On the third hospital day examination by the ophthalmologists revealed for the first time the presence of papilledema with arterial constriction at the disc margins and with engorgement and cyanosis of the veins, but there was no evidence of hemorrhage or exudate. This was considered a sequel to eclampsia.

The patient had now remained in the respirator for more than three days with a temporal pulse ranging between 60 and 108, the temperature ranging from a high of 97.4°, a low of 93° F.

The urinary output diminished progressively from 926 c.c. on the first day to 10 c.c. on the third day.

On the morning of the fourth day the patient quietly expired in the respirator.

Autopsy Findings.—There was noticeable edema over the entire body and particularly of the lower extremities and vulva. Bilateral pleural effusions were present and the lungs were wet and boggy. The heart was normal. The liver was normal in size and showed no subcapsular hemorrhages. The cut surface revealed circumscribed yellowish areas suggesting necrosis, measuring up to 3 mm. in diameter, the right lobe being markedly involved. The pancreas, spleen, kidneys, and adrenals were grossly normal. The uterus contained a single female infant of estimated 24 weeks' gestational age, with beginning maceration. The placenta was implanted on the anterior wall and appeared normal. The lower uterine segment was effaced and the cervix one finger dilated. The brain showed a large, firm, nodular tumor, appearing between the two frontal lobes and measuring about 6 cm. in diameter. The tumor was lying in a hollow, the larger part of which was in the right frontal lobe. None of the tumor reached the base of the brain. The tumor cut with dif-

ficulty and had the typical appearance of a meningioma with a very rough surface. No secondary hemorrhage was noted but there was some swelling of the right frontal lobe (Fig. 1).

Microscopic Report.—The lungs showed a marked bronchopneumonia. Sections of the liver revealed a marked and well-defined coagulation necrosis usually involving the peripheral portion of the lobule (Fig. 2). These lesions were scattered and bore no relation to the capsule. Some were quite large, obliterating tissue relationships. However, in the smaller lesions there was a definite relationship to the periportal area. The early changes were necrosis of cords of liver cells around the periportal space, with hemorrhage, deposition of fibrin, and, in the larger lesions, infiltration of polymorphonuclear leucocytes in the affected area (Fig. 3). The remainder of the liver was well preserved. Sections of the adrenal showed minute focal areas of necrosis in the cortex, with partial loss of cell outline, most prominently seen in the zona fasciculata. There was no hemorrhage in these areas and the remainder of the adrenal tissue was well preserved and normal in appearance.

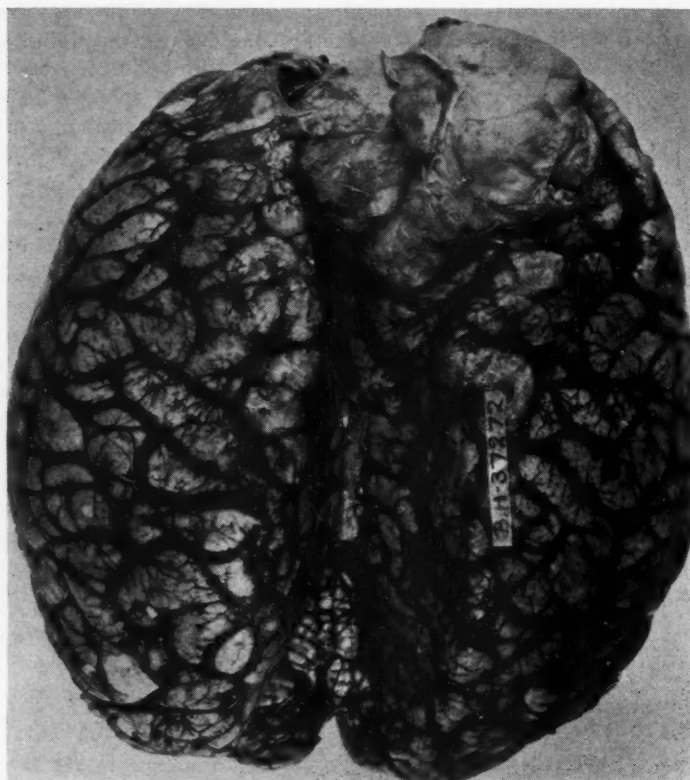


Fig. 1.—Parasagittal meningioma, arising in the right frontal lobe. The tumor was adherent to the meninges and caused considerable edema of this area of the brain.

The kidney showed numerous glomeruli containing very little blood, with an appearance of increased cellularity. In some instances the tuft seemed slightly swollen. There was definite thickening of the substance between the capillary walls; this had the appearance of hyaline change (Fig. 4). Azocarmine stains of the kidney confirmed this as a thickening of the basement membrane in some of the glomeruli (Fig. 5). The tubules showed mild cloudy swelling and granular changes in the epithelium. A rare tubule showed degeneration of the tubular epithelium and a few were lined by regenerated epithelium. Hyaline droplets were also noted in the epithelial cells of a few tubules. Occasional protein casts were noted in the convoluted tubules. There was slight hyalinization of the wall of some of the arterioles but the lumina were not significantly narrowed.

Fig. 2.

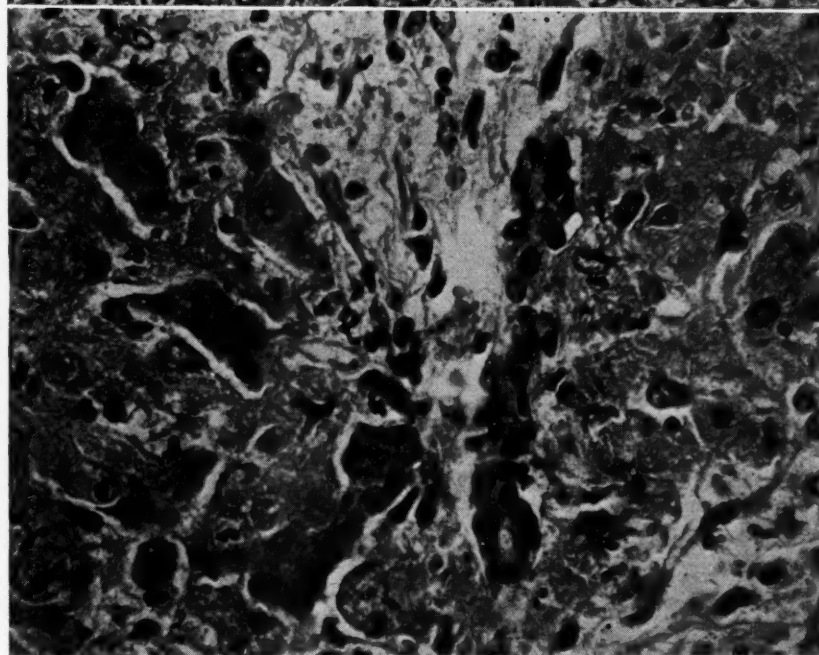
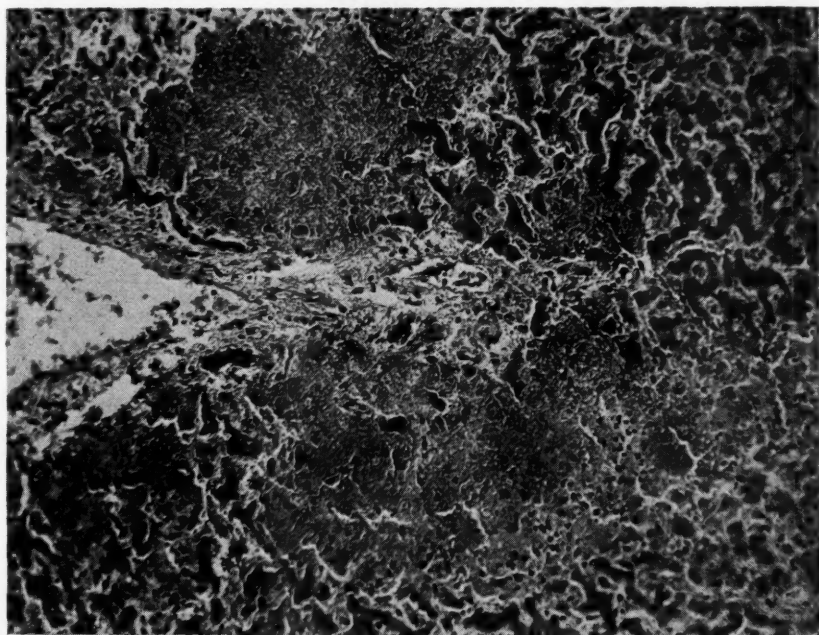


Fig. 3.

Fig. 2—Lesion in the liver, showing hemorrhage and necrosis in the peripheral portion of the lobule. ($\times 163$.)

Fig. 3.—Higher magnification of the liver lesion. Cells in the periportal area are indistinct, and the nuclei are pyknotic or completely destroyed. ($\times 660$.)

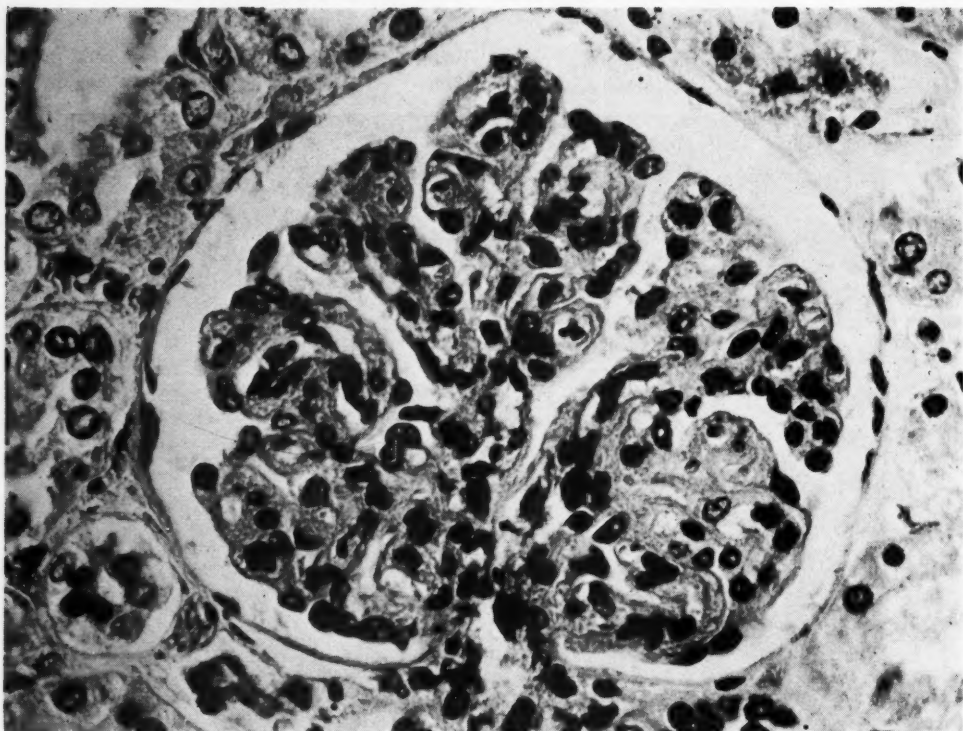


Fig. 4.—Glomerulus showing marked increase in cellularity. The capillaries are collapsed, and contain very little blood. There is an increase in intercellular substance giving the vessels a thick-walled appearance. ($\times 660$.)

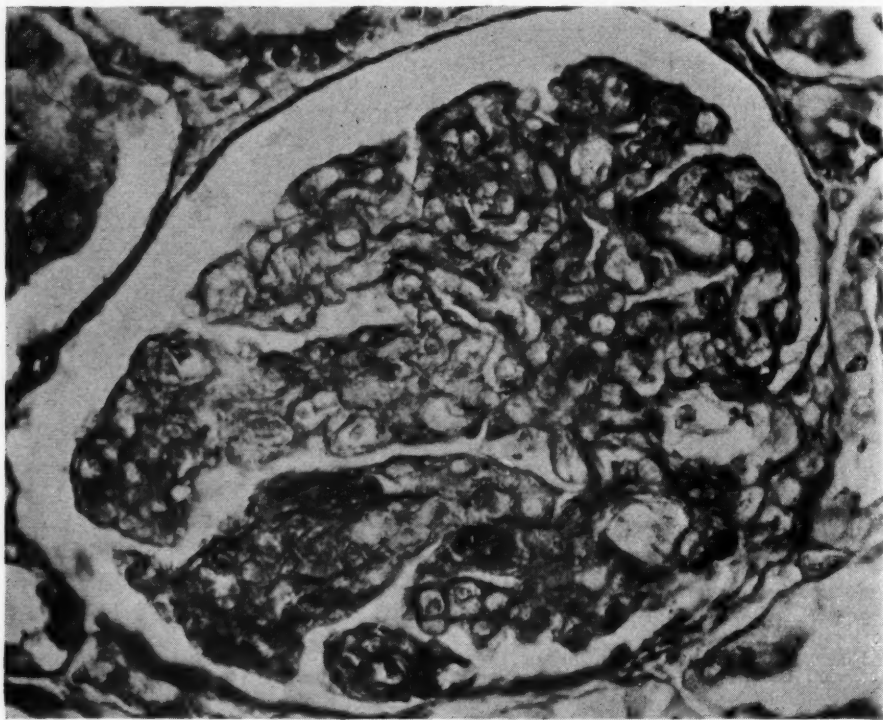


Fig. 5.—Azocarmine stain to demonstrate the basement membrane in a kidney glomerulus. There is a delicate, laminated thickening of this membrane along some of the vessels. ($\times 660$.)

The placenta revealed extensive hyalinization and necrosis. In areas where the villi were relatively well preserved, there was beading of the syncytiotrophoblast, with irregularities in the covering of the villi. However, in most cases the changes were those of marked degeneration.

Sections of the brain showed the tumor to be a fibroblastic meningioma corresponding to Cushing's type 3, variety 1. The tumor was made up of whorls of spindle cells intermingled with collagen fibers. The tumor cells resembled arachnoid cells, with a few psammoma bodies scattered throughout (Fig. 6).

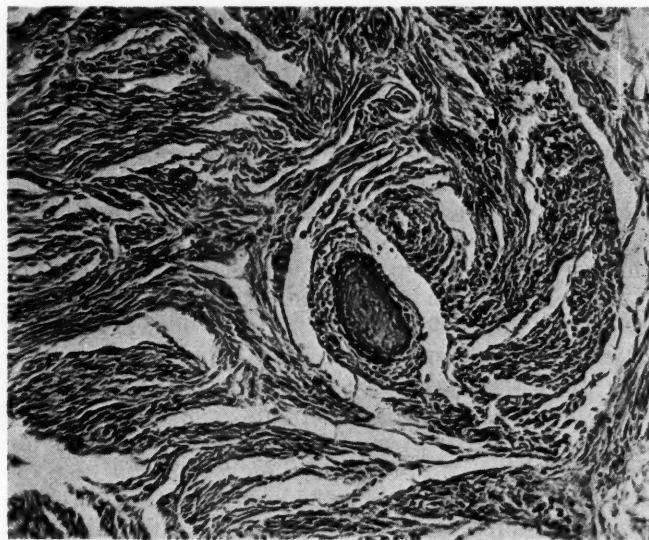


Fig. 6.—Fibroblastic meningioma, with psammoma body at center. ($\times 172$.)

Comment

A diagnosis of eclampsia in this case would depend upon the pathological findings in the liver, adrenals, kidney, and placenta, in addition to the clinical picture. These lesions, once thought to be diagnostic of eclampsia, are now regarded as being somewhat less specific. Eastman¹⁴ states that the characteristic periportal necroses in the liver are not at all constant, and when present are presumably the result of the vascular disturbance. Dexter and Weiss⁸ found liver lesions in only 13 of 25 cases, but described the changes in the kidney as constant and specific for toxemia in all cases. Way¹⁰ regarded the focal necroses in the liver as usually, but not necessarily, located in the periportal areas. He found kidney lesions in all cases, and set forth a quantitative estimation of the pathological change. Acosta-Sison¹¹ found no constant change in liver or kidneys. French¹⁵ recently studied the kidney in toxic oliguria and lower nephron nephrosis, and found that the histopathological changes in the glomeruli were similar to those outlined by Bell¹⁶ in his description of the kidney in eclampsia. The adrenal changes in eclampsia have been emphasized by Way¹⁰ and consist of hemorrhage and necrosis in varying degrees, but not of specific character. The placental lesions have been summarized in the expression "premature aging," and consist of a quantitative increase in syncytial degeneration and stromal fibrosis which take place as term approaches.

It appears that none of these lesions, taken independently, can be regarded as characteristic or diagnostic of eclampsia. However, a combination of these findings in a woman dying after convulsions, hypertension, albuminuria, and edema in the third trimester of pregnancy would be regarded as strongly suggestive of eclampsia. The presence of a large brain tumor during pregnancy

in the case reported, raises the question of whether this clinicopathological picture may be produced by a disease or sequence of events other than toxemia of pregnancy. The findings assume added interest in view of the patient's uneventful antepartum course and the fact that she exhibited no definite signs of toxemia as late as two days prior to her admission to the hospital in a convulsive state.

The rapid onset of convulsions, transitory hypertension, and finally coma, might be easily explained by the presence of a large, irritating, but relatively slow-growing brain tumor. It is not difficult to imagine that a relatively small increase in cerebral edema might be sufficient to make such a growth highly symptomatic.

An equally plausible explanation can be found for most of the tissue changes. Dexter and Weiss⁸ regard as likely the following pathogenesis of the liver lesion: vasospasm of the interlobular branches of the hepatic cords around the periportal space, followed by necrosis and hemorrhage in the affected area. The tissues of the central zone, having a richer collateral circulation, are spared. The present case manifested vasospasm as evidenced by the sudden hypertension on admission, and this was followed by a three-day period in a Drinker respirator in a state of circulatory collapse. Considerable tissue ischemia must have resulted. The kidney lesions, glomerular and tubular, resemble in mild degree those seen after periods of ischemia and anuria from other causes (lower nephron nephrosis). The minute necroses in the adrenals in this case are no more than might be expected from prolonged ischemia.

It should be noted that the patient in this case was subjected to alternate positive and negative pressure in a Drinker respirator for a period of three days. In 1932 Theobald¹⁷ was able to produce periportal necrosis of the liver in dogs anesthetized with equal parts of chloroform and ether, by increasing the intra-abdominal pressure to 80 to 100 cm. saline for short periods of time. On the basis of this work he regarded the sudden increase in intra-abdominal pressure caused by a convulsion as a likely cause for the liver lesions of eclampsia. Subsequently Strauss and Maddock¹⁸ repeated these experiments, and showed that the lesions produced bore more relation to chloroform anesthesia than to increase in intra-abdominal pressure, and in any case were not similar to those seen in eclampsia. It is by no means certain that the pressure exerted by the respirator had any effect on the liver of this patient.

In considering the pathological significance of the lesions described, it is interesting to recall one of the cases reported by Acosta-Sison.¹¹ The patient entered the hospital because of intermittent bleeding due to placenta previa. Her blood pressure was 107 systolic, and she had no visual disturbances, headache, or edema. A dose of Pituitrin (0.25 c.c.) was given, and "five minutes later she became rigid and cyanosed with frothing at the mouth. The pulse then became filiform, the respirations irregular, and death rapidly supervened. At autopsy there were found extensive hemorrhagic necrosis of the liver and marked parenchymatous degeneration of the visceral organs. The pathological diagnosis was eclampsia." The patient apparently had no warning signs or symptoms before the onset of convulsions, which were followed quickly by death, yet the pathological findings (which are not described) were sufficient to warrant the inclusion of this case in the author's work on pathology of eclampsia.

The difficulty in making a clinical diagnosis is well brought out in our case report and needs no further comment. It is noteworthy that the sudden onset of symptoms and lack of response to therapy, in a woman believed to be only 24 weeks pregnant, was regarded as atypical of eclampsia, but did not lead to a diagnosis of brain tumor by numerous observers. Furthermore, papilledema, which on at least one reported occasion led to a mistaken diagnosis of brain tumor⁴ did not appear in this case until just before death. The

use of an electroencephalogram for the differentiation between convulsions due to eclampsia, brain tumor, and epilepsy has been suggested by Rand and Andler.¹ It is possible that such a procedure might have led to a correct diagnosis in this case, but it is hardly a feasible routine to be carried out on women in eclamptic convulsions.

We do not believe a final decision can be reached as to whether the case presented was one of eclampsia, as well as a brain tumor complicating pregnancy. The histopathological findings in eclampsia can no longer be regarded as specific. They may be produced by a combination of vasospasm, followed by ischemia, in the pregnant woman. Toxemia of pregnancy is, of course, by far the most common disease process capable of producing this combination. However, brain tumor in pregnancy must be considered as a possible causative agent in the production of a clinical and pathological entity identical to eclampsia. This is particularly true when death is preceded by a long period of coma and probable tissue ischemia.

Summary

1. A case is presented of convulsions, hypertension, albuminuria, and edema in the twenty-fourth week of pregnancy, followed by coma and death after three days in a Drinker respirator. Autopsy showed lesions characteristic of eclampsia and a large meningioma of the right frontal lobe.

2. A partial review of the literature shows that a relatively small number of cases of brain tumors in pregnancy are on record, probably less than fifty.

3. No previous case was noted in which brain tumor was present in a pregnant woman with clinical and pathological findings of eclampsia.

4. Lesions of the liver, kidneys, adrenals, and placenta in eclampsia are probably the result of vasospasm and tissue ischemia.

5. Brain tumor occurring in pregnancy may exactly simulate the clinical picture of eclampsia, and under certain conditions may cause pathological changes in the visceral organs similar to those of eclampsia.

The authors wish to acknowledge the helpful assistance given them by Dr. Sigmund Wilens, Dr. John Hall, and Dr. Louis B. Stevenson in the preparation of this case report.

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URETERAL OBSTRUCTION IN CARCINOMA OF THE CERVIX

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IN OUR year-by-year association with patients having carcinoma of the cervix at the University of Michigan Hospital, we have been impressed with the large number who develop pathologic conditions of the urinary tract. Changes in the bladder or urethra secondary to irradiation or extension of the neoplasm are common. Our interest here, however, is primarily concerned with the problem of ureteral obstruction.

The reported incidence of ureteral obstruction and subsequent death from uremia has varied considerably with different investigators. It is usually agreed, however, that ureteral obstruction and terminal uremia are a common eventuality. De Alvarez,¹ in a review of the University of Michigan Hospital autopsy series, found that 40 per cent of patients with cervix carcinoma died of uremia. Herger and Schreiner² reported that 53 per cent of their autopsy series revealed stricture of one or both ureters. Diehl and Hundley³ recently have indicated that 38 per cent of a group of 37 patients showed some degree of ureteral dilatation one year after therapy.

For many years there has been a difference of opinion concerning the cause of ureteral obstruction. Several factors may, of course, play a part in its production. First, it may be caused by extension of the neoplasm and either compression or infiltration of the ureter by carcinoma with resulting obstruction of the lumen. Second, it may be caused by changes secondary to irradiation. This might be manifest by edema which develops during or immediately following therapy or by fibrosis and scarring some time later. Everett⁴ has subscribed to this latter theory. In 1934, he reported eleven out of eighteen patients with ureteral obstruction secondary to irradiation for carcinoma of the cervix. One should also not overlook the fact that infection may be an important factor in the production of ureteral stricture.

We have long considered the possibility of active early surgical management of the ureters (i.e., transplantation into bowel, nephrostomy, or cutaneous ureterostomy) when evidence of ureteral obstruction is first demonstrated. Any procedure which might hope to prolong the life of 40 to 50 per cent of these patients now dying of uremia should be given serious consideration. In order to accumulate additional data regarding ureteral obstruction this study of patients with cervix carcinoma was planned and carried out.

It was hoped that by careful analysis of the records of a large group of patients we might again determine the incidence of obstruction. We hoped also to learn whether the incidence of obstruction before death varied significantly from the incidence observed in the autopsy series. A comparison of these two groups might indicate how many patients actually die from obstruction. Furthermore, it seemed desirable to determine the actual cause of the obstruction. In carrying out our work we have studied sections of ureters

taken at the time of autopsy to determine whether compression or changes due to irradiation could be discovered. We have also studied the records of the patients to determine whether there existed any relationship between clinical course and therapy or change in the extent of the disease. Finally, we have tried to evaluate the results of our present management of patients with evidence of ureteral obstruction. Have the cases which we treated by ureteral dilatations or nephrostomy done better than the untreated group?

Material

The group studied includes all cases of cervix carcinoma seen in the gynecologic service from January, 1942, to January, 1947. The total of 458 patients were distributed according to clinical groups as outlined in Table I.

The clinical groupings were determined by the following criteria:

Clinical Group I.—Very small and early, histologically proved carcinoma of the cervix, such as intraepithelial lesions and carcinoma arising in a cervical polyp. In general use, these are the early commonly unrecognized cases.

Clinical Group II.—Clinically recognizable, histologically proved carcinoma of the cervix, exclusive of Clinical Group I lesions, still entirely confined to the cervix and without evidence of parametrial thickening or vaginal infiltration.

Clinical Group III.—Histologically proved carcinoma of the cervix with questionable parametrial thickening. The cervical lesion proper may or may not be extensive, the important feature of this group being the question of parametrial involvement. Into this group are placed those patients concerning whom there might well be a difference of opinion regarding extension into the adjacent tissues.

TABLE I. TOTAL NUMBER OF PATIENTS WITH CARCINOMA OF THE CERVIX FROM JANUARY, 1942, TO JANUARY, 1947, ACCORDING TO CLINICAL GROUP

Clinical Group	I	30
	II	43
	III	59
	IVa	173
	IVb	153
Total		458

Clinical Group IV.—All histologically proved carcinomas of the cervix revealing definite parametrial thickening or invasion of the vagina. For convenience and statistical comparison these advanced cases are subdivided as follows:

IVa: Any carcinoma of the cervix presenting definite extension beyond the cervix. This may be parametrial thickening or invasion of the vaginal wall and the involvement may be unilateral or bilateral.

IVb: Advanced carcinoma of the cervix with complete fixation (frozen pelvis) on one or both sides and/or metastasis either local or remote.

The clinical grouping is based on the initial examination when the patient is first seen at our hospital. In developing our clinical grouping we have attempted to recognize the fact that the early lesion is the important one (Clinical Group I). We have also recognized the questionable case in which it is difficult or impossible to determine accurately the presence or absence of parametrial thickening (Clinical Group III).

We have recently again revised our clinical grouping so that it can be more accurately compared to the League of Nations Classification. For purposes of comparison as far as this study is concerned, our Clinical Groups I, II, and III

are all included in the League of Nations I, while our clinical Group IVa is equivalent to League of Nations II. Clinical Group IVb includes League of Nations III and IV. In an effort to make it more convenient to convert to our classification to that of the League of Nations we now have replaced the terms IVa and IVb with IV, 2, IV, 3, and IV, 4.

Of the total group of 458, there were pyelographic studies on 333. Two hundred nineteen revealed normal pyelograms. One hundred fifteen showed abnormal pyelograms. (By abnormal pyelograms is meant either hydronephrosis or nonvisualization as demonstrated by intravenous or retrograde pyelography.) Of the group having pyelograms 34 per cent showed evidence of obstruction. We have omitted all pyelogram interpretations including mild grades of hydronephrosis which were of doubtful significance. The distribution is shown in Table II.

TABLE II. TOTAL NUMBER OF PATIENTS HAVING PYELOGRAMS, NORMAL AND ABNORMAL, JANUARY, 1942, TO JANUARY, 1947

CLINICAL GROUP	TOTAL	NORMAL	ABNORMAL
I	7	7(100%)	0
II	22	20(91%)	2(9%)
III	43	36(84%)	7(16%)
IV a	134	104(78%)	30(22%)
IV b	127	52(41%)	75(59%)
Total	333	219(66%)	144(34%)

The gross survival rate in the abnormal-pyelogram group was 16 per cent as compared to 62 per cent in the normal-pyelogram group. While the percentage survival shows a decrease in the more advanced clinical groups, the survival is decidedly less in the abnormal pyelogram group. This indicates the importance of ureteral obstruction in determining the prognosis for any one patient. This comparison is represented graphically in Table III.

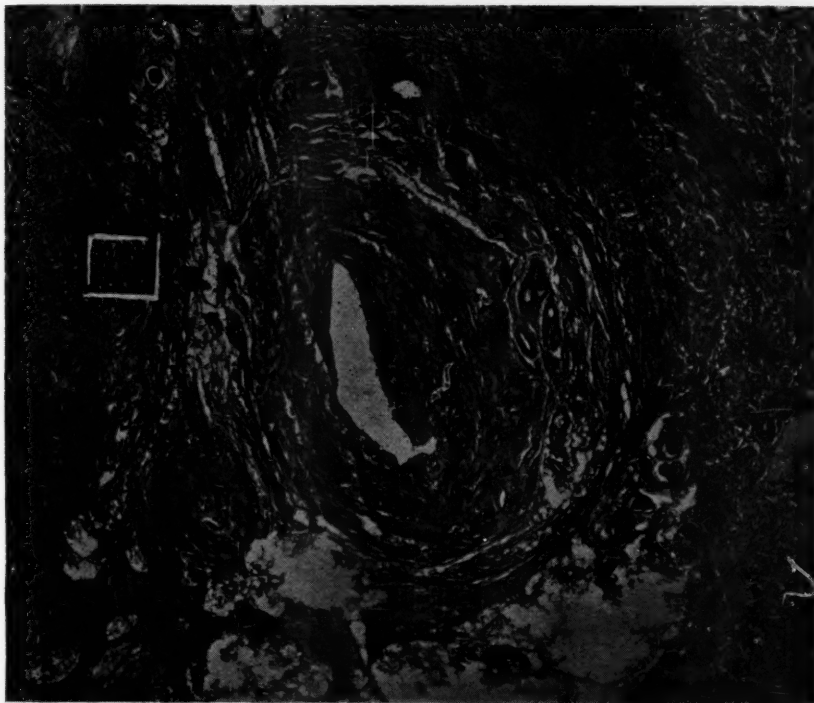
TABLE III. COMPARISON OF SURVIVAL RATES IN NORMAL AND ABNORMAL PYELOGRAM GROUPS

CLINICAL GROUP	NORMAL PYELOGRAM	GROSS SURVIVAL ALL CASES 1942 TO 1946	ABNORMAL PYELOGRAM
I	71%	97.5%	--
II	75%	82.5%	50%
III	77%	77.3%	14%
IV a	61%	64.4%	27%
IV b	46%	31.0%	12%
Total	62%	58.6%	16%

At the autopsy table, patients dying of uremia have demonstrated thickening and nodulation of the broad ligaments. This is often extensive enough to form a solid bridge of tissue extending from one wall of the pelvis to the other in which all organs are fixed (frozen pelvis). The ureters may be visualized passing into this mass after they enter the true pelvis. Dilatation of the ureters usually begins at the margin of the tumor mass which fills the pelvis. The lumen of the ureter is relatively constricted as it courses through the mass. It is not necessary to have complete stenosis of the ureter before dilatation may develop above.

Upon microscopic section of this mass one might expect to find that it contains either inflammatory tissue, neoplasm, or fibrous tissue. The sections which we have studied have usually demonstrated neoplasm. Fig. 1, A shows a cross section of ureter as it passes through a mass of neoplasm. There was

A.



B.

Fig. 1.—A, Cross section of the left ureter as it passes through the base of the broad ligament. It is surrounded by squamous-cell carcinoma. Above this the ureter was involved in a massive pyelohydronephrosis.

B, High power showing detail of the carcinoma cells.

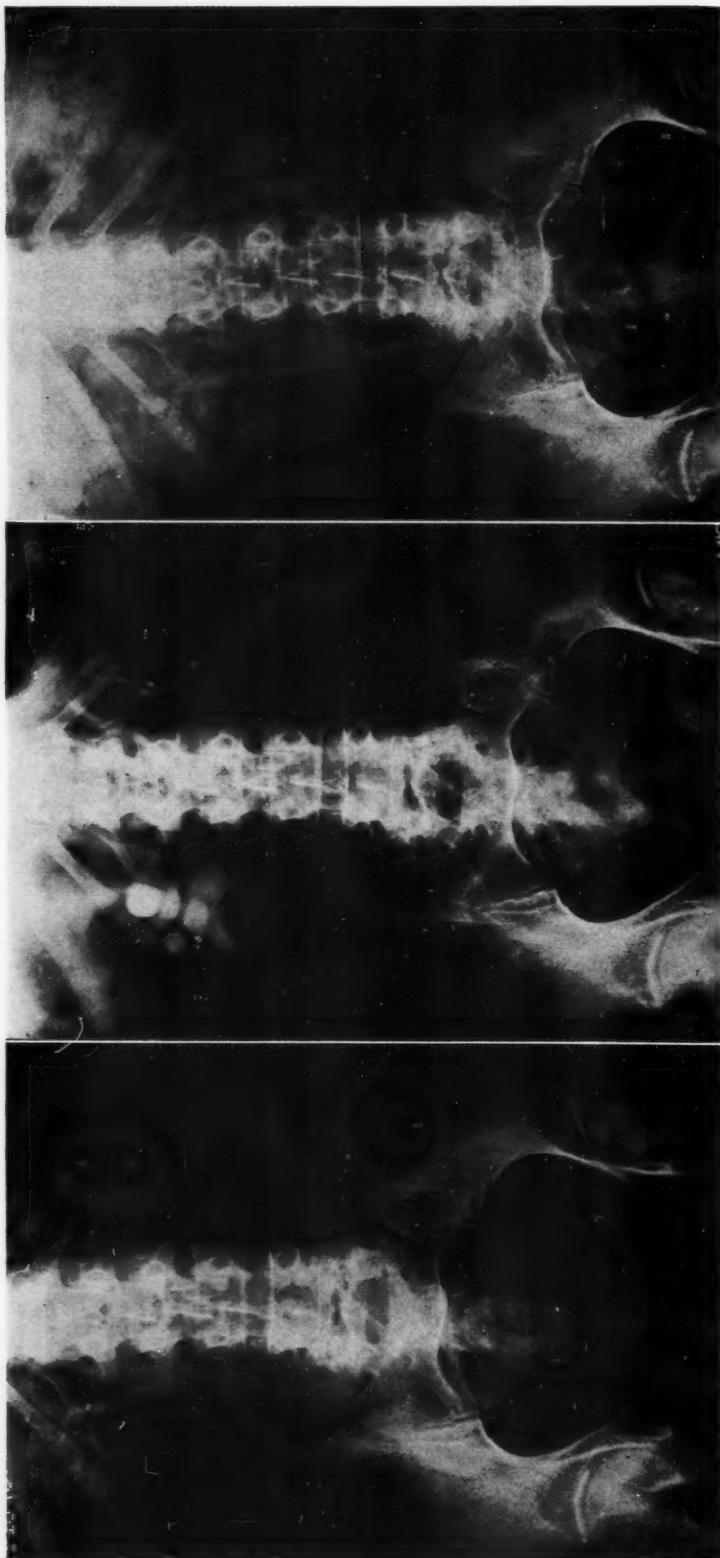


Fig. 2.

Fig. 2.—Mrs. V. M. (No. 536444). Normal pyelogram on Nov. 10, 1943, at the time of initial irradiation.

Fig. 3.—Mrs. V. M. (No. 536444). Intravenous pyelogram on June 10, 1944. Normal left pyelogram; 2 plus right hydronephrosis.

Fig. 4.—Mrs. V. M. (No. 536444). Intravenous pyelogram on March 11, 1947. The right pyelogram is now normal; however, there is non-visualization on the left indicating autonephrectomy.

massive pyelohydronephrosis above this level. The ureter can be seen surrounded by neoplasm. No scarring or fibrosis can be seen. Fig. 1, *B* is high power, and shows the cancer cells more clearly.

Further effort to determine the cause of ureteral obstruction was made by study of the patients' records for specific clues. For instance, we were interested in knowing how many times evidence of obstruction was found opposite the side of greatest palpable pelvic involvement. This situation was noted in five cases, but on closer analysis the findings were seen to be equivocal in all but one case. In this one case, the patient developed a *left* pyelohydronephrosis which required nephrectomy nine months after treatment and died elsewhere six months later; yet, on repeated examination by several members of the staff, the *right* adnexal region consistently showed more thickening. We are more impressed with the number of patients consistently showing ureteral obstruction on the side of greatest pelvic involvement.

Repeated pyelograms showed either progression or improvement in thirty patients. Twenty-five demonstrated progression and only one of this group remains alive. Five showed regression of the obstruction and four of these are still alive. There was no patient with progression of hydronephrosis who did not also have advanced and progressing neoplastic involvement of the pelvis.

The findings in one case are of sufficient interest to warrant reporting here. Mrs. V. M. (No. 536444) had a diagnosis of carcinoma of the cervix, Clinical Group IVa, made on Nov. 9, 1943. At that time thickening was felt to be most marked on the *left*. She received 2,200 r to each of four pelvic ports from Nov. 9, 1943, to Dec. 5, 1943. On December 6, 90 mg. of radium were implanted for 60 hours or a total dose of 5,400 mg. hr. Pyelograms were negative at this time (Fig. 2). In June, 1944, six months later, a 2 plus hydronephrosis was found on the *right* side (Fig. 3). A colostomy was performed because of severe irradiation proctitis. No treatment of the hydronephrosis was instituted. On March 11, 1947, a normal right pyelogram was noted. However, a left autonephrectomy had developed (Fig. 4). She has shown extensive infiltration bilaterally since June 10, 1944. Her condition at present is fair with no elevation of the nonprotein nitrogen. By way of explanation it is suggested that the obstruction on the right might have been due to edema and infection following therapy and later on this regressed. Obstruction on the left then developed due to extension of the neoplasm.

Another case is also of interest because it demonstrates the actual clearing of ureteral obstruction following irradiation with no further treatment. Mrs. S. B. (No. 511544) was seen first on Sept. 3, 1942, and a diagnosis of carcinoma of the cervix, Clinical Group IVb, was made. Pelvic examination revealed bilateral pelvic involvement with fixation. She received a full course of external irradiation beginning on September 5. On September 16, pyelograms revealed a 2 plus hydronephrosis bilaterally (Fig. 5). Because of this finding, radium therapy was omitted. Attempts at ureteral dilatation were unsuccessful on Sept. 23 and Sept. 28, 1942. On Jan. 21, 1943, the left pyelogram was negative and the right had almost cleared (Fig. 6). Pelvic examination at that time revealed less thickening bilaterally and no fixation. Normal pyelograms were obtained on March 2, 1944 (Fig. 7). The patient is alive on last follow-up and her condition is reported as satisfactory.

Until recently it has been our policy to dilate the ureters when unilateral hydronephrosis was present. Nephrostomy is performed when bilateral obstruction is present and the neoplasm is not progressing so far as can be determined clinically. The patient's general condition would, of course, have to be such as to permit operation. Nephrectomy is considered only when symptomatic pyelohydronephrosis is present.

Certain interesting facts regarding ureteral dilatation have come to light. Of the nine patients receiving dilatation, one remains alive. In the group of

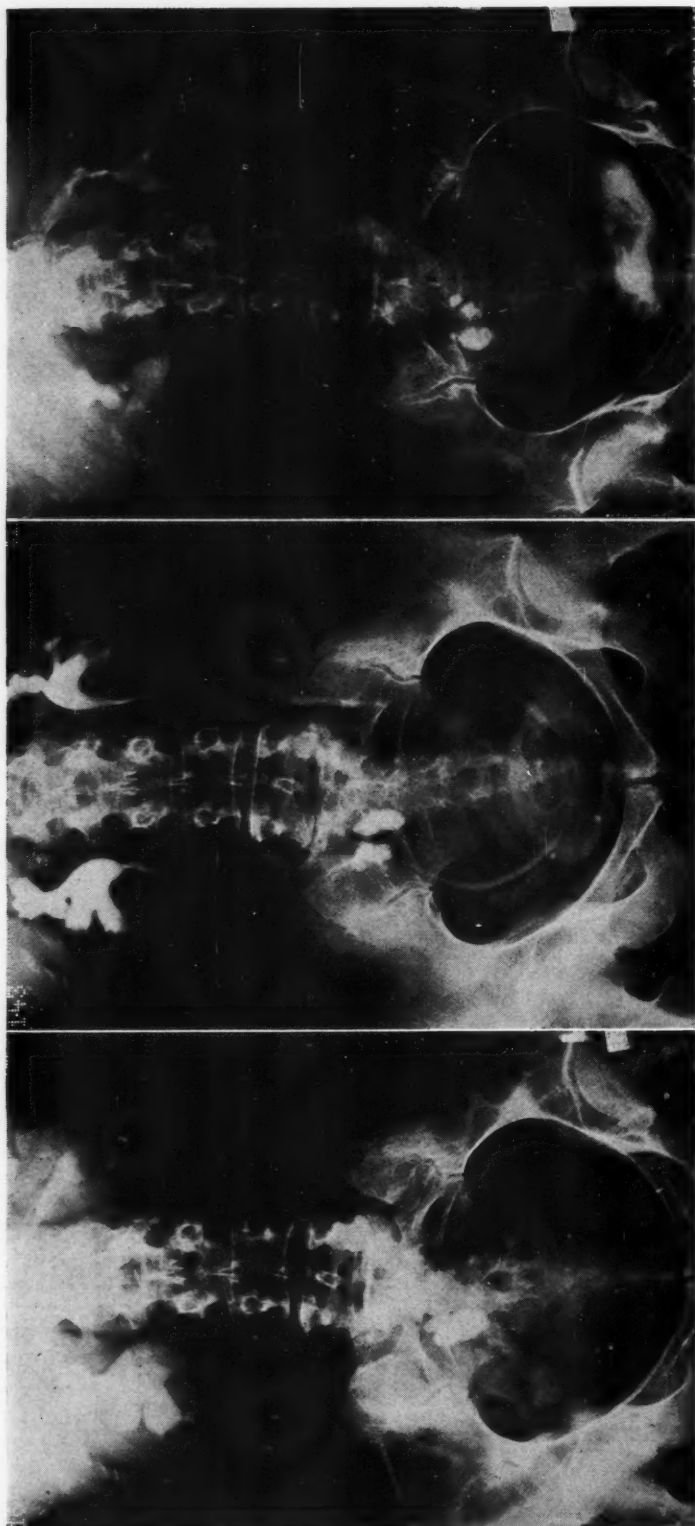


Fig. 5.

Fig. 5.—Mrs. S. B. (No. 511544). Intravenous pyelogram on Sept. 16, 1942, at the time of initial irradiation, indicating a 2 plus hydro-nephrosis bilaterally. A calcified lymph node can be seen overlying the sacral promontory.

Fig. 6.—Mrs. S. B. (No. 511544). Intravenous pyelogram on Jan. 21, 1943. The left pyelogram is now normal and there is almost complete clearing on the right.

Fig. 7.—Mrs. S. B. (No. 511544). Normal intravenous pyelogram on March 2, 1944.

Fig. 6.

Fig. 7.

patients who died, the average interval between dilatation of the ureter and death was eight months. The shortest interval was one month, the longest fifteen months. Three of the five patients showing regression of obstruction had ureteral dilatations. Yet dilatation of the ureter did not appear to be of benefit. Only one of the nineteen surviving patients in the abnormal-pyelogram group had dilatations. Our results, at least, suggested that the trauma incident to dilatation might actually increase edema and stenosis and hasten the development of autonephrectomy.

Three patients had nephrostomies. All of these were performed on patients with plasma nonprotein nitrogen levels ranging from 88 to 163 mg. per cent preoperatively. Except for the uremia, their general condition was satisfactory. All of them had advanced cervix carcinoma. Although the nonprotein nitrogen was not in any case over 43 mg. per cent postoperatively, all three patients died in one, two, and seven months, respectively. The cause of death is not known since it occurred elsewhere. Nephrostomy performed on patients such as these (i.e., with advanced neoplasm and uremia) apparently does not materially improve prognosis.

Comment

This study reveals a close correlation between the incidence of ureteral obstruction as determined by pyelograms (34 per cent) and the incidence of uremia as a cause of death in our autopsy series (40 per cent). This tends to confirm the findings of others, that ureteral obstruction resulting in uremia is one of the important causes of death from carcinoma of the cervix.

By taking roentgenograms with radium applied to the cervix and ureteral catheters in place, and with the vagina tightly packed in our routine manner, we have found that the ureters often pass as close as 1 to 2 cm. to the source of irradiation. During the years covered in this study, our customary radium application consisted of a tandem tube in the uterus and cervix with 20 mg. and 30 mg. in the cervix; together with a 20 mg. capsule in each lateral fornix for a total dose of approximately 5,000 mg. hr. (0.5 mm. platinum equivalent filtration). Recently, by increasing the amount of radium implanted to 100 mg., the dosage has been increased to approximately 6,000 mg. hr. We feel that the ureters are subjected to a significant amount of irradiation. In this study, however, we have not been able to demonstrate that irradiation commonly causes stricture of the ureter. Actually, quite the reverse has been true. Our findings indicate that obstruction is usually due to extension of the neoplasm. We have observed regression of hydronephrosis with decrease in demonstrable pelvic neoplastic involvement after x-ray therapy in one instance. Furthermore, whenever ureteral obstruction developed there was an associated clinical advancement of the neoplasm. We also noted that obstruction of the ureter commonly develops on the side of greatest palpable pelvic involvement. While our experience does not allow us to state that irradiation never plays a part in the etiology of ureteral obstruction, it would seem that obstruction is more often due to the extension of the neoplasm.

Everett's recent review of his experience⁵ tends to indicate that ureteral obstruction due to irradiation is greatly dependent upon the radium dosage. Until 1939 he used a large amount of radon (3.0 Gm.) for a short exposure of one hour or a total dose of 3,000 mg. hr. In this series of patients he observed ureteral obstruction in 48.4 per cent. However, when the amount of radium administered was diminished even though the total dose was increased (two applications of 100 mg. radium for 24 hours, two weeks apart for a total of 4,800 mg. hr.) "there were no urological lesions which could be conclusively attributed to irradiation." External irradiation had not been changed radi-

cally. His total dose (2,500 r to each of four pelvic ports) is slightly higher than ours. Ureteral obstruction due to irradiation is unusual in our series because the dose has not been great enough to cause stenosis.

Our treatment of ureteral obstruction, whether it be by ureteral dilatation or nephrostomy, has not improved prognosis. Although uremia is a common cause of death in cervix carcinoma, there are those who prefer not to divert the urinary tract since they feel that, by so doing, nothing would be accomplished but the substitution of another less pleasant cause of death.

We feel, in light of this study, that diversion of the urinary tract when bilateral obstruction is first noted would give better results than we have had with this type of procedure in the past.

Conclusions

1. Our incidence of ureteral obstruction in all cases of carcinoma of the cervix is 34 per cent. This agrees closely with the reported incidence of obstruction as found at autopsy (40 per cent).

2. Our evidence points to the fact that the cause of obstruction to the ureters is extension of the neoplasm.

3. From the long-range therapeutic standpoint ureteral dilatation is not indicated, and if used at all should be restricted to the alleviation of pain of a unilateral hydroureter hydronephrosis only during or shortly after x-ray therapy.

4. Early diversion of the urinary tract, either by ureterosigmoid transplants or cutaneous ureterostomy, would seem to be preferable to late nephrostomy drainage.

5. Nephrostomy is indicated in patients having pyelohydronephrosis.

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118 EAST COLLEGE AVENUE.

PROPHYLACTIC PENICILLIN DURING LABOR IN INFECTION-PRONE PATIENTS

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AS A prophylactic agent the antepartum use of the sulfonamides has proved to be disappointing, due to difficulties in administration and the maintenance of effective blood levels during labor. Moreover, these drugs were not sufficiently free of danger to be used generally as preventive treatment before delivery. On the other hand, penicillin, being comparatively easy to give and having definitely fewer objectionable qualities, has had more extensive acceptance.

Although penicillin is no doubt deserving of some of the considerable use in labor to which it has been put, there is as yet a remarkable paucity of reliable information regarding the probable degree of protection to be expected. This is not to deny that there are now many articles on the subject, but most of these express an optimism which seems to be suggested by the results obtained with penicillin in other situations rather than by the scant data presented on its use in labor. There are, however, several exceptions. In 1948 Woltz and Stashak¹ reported on 57 patients with premature rupture of the membranes of whom 29 received 12,500 units of penicillin every 3 hours until delivery. Only 2 had puerperal infection, whereas 6 of the 28 controls without penicillin had febrile puerperia. It is noteworthy, though, that cultures from the cervixes showed instances of penicillin-sensitive as well as penicillin-resistant organisms in both treated and untreated cases. Keettel, Scott, and Plass² reported a series of vaginally delivered women of whom alternate patients "so far as practicable" received from 300,000 up to 900,000 units of penicillin while in labor, and another dose 18 to 20 hours post partum. Among the 430 untreated controls there was an incidence of 10.2 per cent with 2 or more days of puerperal fever (100.4° F. or higher); whereas, only 4.7 per cent of those treated were febrile. Therapeutic levels of penicillin found in the amniotic fluid suggested to them some fetal protection against infection, though this was not evident from the data available in their series. A later series by Keettel and Plass³ gave essentially the same results. Guilbeau, Schaub, and Andrews⁴ took cultures from the uterus 36 to 72 hours post partum in 54 patients treated in labor with 200,000 to 400,000 units of penicillin, and in 32 without penicillin. The incidence of absolutely sterile cultures was 59.4 per cent in the treated as opposed to 6.2 per cent in the untreated cases. Only one patient with penicillin had a febrile puerperium.

Starting in 1947 an experiment was conducted at Herman Kiefer Hospital which differed from those mentioned in the fact that it was concerned with a group of patients in whom there was to be expected an unusually high incidence of infection and who, therefore, had a real need for prophylaxis. These were patients with prolonged labor, long rupture of the membranes before delivery, or both. The test was conducted as follows.

Material

The material was made up of 200 patients delivered from the twenty-eighth week of pregnancy to full term, who were selected (from a total of approximately 5,500 clinic obstetrical admissions) because they had premature rupture of the membranes for at least 20 hours, labor for 20 hours or longer, or both. Patients with definite extragenital infections before delivery, and those later delivered by cesarean section were excluded. One-half of the patients were carried through labor as controls without penicillin or other antibiotics. The other 100 were given penicillin in 30,000 unit doses every 3 hours from approximately the twentieth hour until delivery; or in some from the time of admission, if premature rupture of the membranes or the onset of labor could be established as occurring 20 or more hours before. As Herman Kiefer Hospital receives many referred clinic patients, the latter group was substantial and included a number of already infected and sometimes seriously ill patients. In order to obtain more clear-cut evidence regarding the prophylactic effect of penicillin, its administration was discontinued promptly at delivery, to be resumed (along with the other usual treatment) only if definite puerperal infection occurred. Controls who developed puerperal infection received the same treatment.

Penicillin given as mentioned above naturally resulted in a great variation of dosages, ranging from one injection up to a maximum of 35 doses, or a total of 1,050,000 units. In view of what is now known, the possibility that some infections among the controls might have been avoided with penicillin prophylaxis cannot be denied, and perhaps the same can be said regarding the discontinuance of the treatment promptly at delivery in the other, or treated group. However, the only maternal death in connection with the experiment occurred from hemorrhage and shock about 2 hours after delivery in a patient who had received prophylactic penicillin during labor. This case was not included in the series since for statistical purposes there was no puerperium.

Temperatures were taken by mouth every 4 hours while the patients were in labor, at least 4 times a day if the patient was admitted after rupture of the membranes but before labor, and the same during the puerperium. A temperature rise up to 100° F. or over was the criterion for a diagnosis of antepartum infection. As noted above, the few patients with extragenital infections before delivery were excluded from the study. The criterion for puerperal fever was a temperature elevation of 100.4° F. (38° C.) or over, excluding the first 24 hours after delivery. If there was a period of only 24 hours or less with puerperal fever, the patient was listed as having one-day fever; whereas, the occurrence of such fever on 2 or more days (whether consecutive or not) was considered to be sufficient evidence of puerperal infection. As is customary, an attempt was made to differentiate between puerperal and extragenital causes of postpartum fever. Urinary-tract infection was diagnosed several times, but in every instance along with definite or probable evidences of puerperal uterine infection. Respiratory infections seemed to have been eliminated as a cause of postpartum fever by the exclusion from the series of those patients who were febrile before delivery due, or presumably due, to extragenital causes. The entire absence of puerperal mastitis as the sole cause of fever was probably largely due to the fact that the great majority of the patients were sent home in 5 to 7 days and therefore before the usual time for breast infections.

For the sake of further information regarding antepartum infection, the placentas from both the treated and the control groups were examined for in-

flammatory leucocytic infiltration of the placental amnion, chorion, and umbilical cord. Previous studies^{5, 6} have demonstrated good evidence that these changes are due to antepartum invasion of the uterus by pyogenic bacteria. Moreover, such inflammation, even in the absence of intrapartum fever, was followed by definitely increased incidence of postpartum infection. Consequently, in the present study it was thought that the data from the placental examinations might lead to additional information regarding the efficacy of penicillin prophylaxis.

It should be stated that the investigation at the start was planned to consist of a strict alternation of a series of patients, one with and the next without penicillin ante partum. It soon became evident, however, that this was an unobtainable ideal, due, for one thing, to the impossibility of determining in some cases whether or not the membranes had ruptured, and in others the existence or not of true labor. Of more importance was the same difficulty experienced by Keettel, Scott, and Plass; that is, the uncontrollable tendency to place the more seriously ill patients among those who were to receive penicillin. As a consequence, the two groups are far from mathematically comparable, and this should be taken into consideration in appraising the results. Table I demonstrates some of the differences in the two groups.

Among those treated prophylactically with penicillin before delivery there is a greater proportion of more severe cases. Percentages are the same as the numbers given.

TABLE I

	HOURS OF LABOR OR PREMATURE RUPTURE OF MEMBRANES				ANTE-PARTUM FEVER	PLACENTAL INFLAMMATION
	20-40	40-60	60 AND OVER	AVERAGE		
With Penicillin	36	26	38	71	33	61
No Penicillin	48	21	31	53	11	58

Maternal Results

In Table II are shown the incidences of puerperal infection and one-day fever in the prophylactically treated and the untreated patients. In marked contrast to the report of Keettel, Scott, and Plass, there was a striking reduction in the incidence of one-day fevers with penicillin. On the other hand, the gross figures, without allowance for the differences (Table I) in the two groups, would seem to offer little or no advantage in the use of penicillin so far as two-or-more-day fevers (puerperal infection) were concerned.

TABLE II

	PUERPERAL INFECTION	ONE-DAY FEVER
100 with penicillin	10	3
100 without penicillin	8	14

However, due to uncontrollable selection of patients as noted before, the group receiving prophylactic penicillin had a much greater proportion of patients with antepartum infection as evidenced by temperature elevations of 100° F. or over; a larger number of those with excessively long rupture of the membranes and prolonged labor; and a few more who had inflammation of the placenta (Table I). In general, it is to be expected that patients with such conditions will inevitably have a higher incidence of puerperal infection. Moreover, it is in just such patients that infection offers a greater hazard be-

cause of loss of resistance from exhaustion and also because of the frequent necessity for operative delivery with its tendency toward lowered resistance by additional blood loss and shock. Consequently, it was encouraging that penicillin in labor appeared to have a definite prophylactic efficacy in those patients with a greater liability to infection in the puerperium, as demonstrated in Table III.

TABLE III

	WITH PENICILLIN			WITHOUT PENICILLIN		
	TOTAL CASES	PUERPERAL INFECTION	ONE-DAY FEVER	TOTAL CASES	PUERPERAL INFECTION	ONE-DAY FEVER
Antepartum fever	33	4 (12.1%)	3 (9.1%)	11	3 (27.3%)	1 (9.1%)
Premature rupture of membranes or labor for 60 hours or over	38	2 (5.3%)	3 (7.9%)	31	4 (12.9%)	5 16.1%
Inflammation of the placenta	61	6 (9.8%)	3 (4.9%)	58	7 (12.1%)	9 (15.5%)
All 3 of above	13	1 (7.7%)	3 (23.1%)	6	1 (16.7%)	1 (16.7%)

Table III shows the incidence of postpartum infection with and without prophylactic penicillin in patients having conditions especially predisposing to such infection.

From the standpoint of prevention, there would seem to be rather questionable value in a comparison of the seriousness of the puerperal infections which actually did occur in the prophylactically treated and in the untreated groups, since in either case a similar response to the same curative postpartum treatment should be expected in both. Keettel, Scott, and Plass found this to be approximately the case in regard to the duration of the infection, the slight advantage for the prophylactically treated patients being probably easily explainable by the fact that they also received another dose 18 to 20 hours after delivery. Taking the highest temperature elevation as a gauge, in the Herman Kiefer Hospital series, it is seen from Table IV that the antepartum prophylactic use of penicillin had no significant effect on the severity of the puerperal infections which did occur. As stated before, no patient died of infection in this series.

TABLE IV

	100.4° TO 100.9° F.	101° TO 101.9° F.	102° TO 102.9° F.	103° F. AND OVER
Prophylactic penicillin before delivery	0	7	2	1
No penicillin before delivery	1	5	0	2

Table IV shows the highest temperatures in puerperal infection cases (100.4° F. or over for at least 2 days, excepting the first day) with and without antepartum prophylactic penicillin.

The partial effectiveness of antepartum prophylactic penicillin in reducing the incidence of puerperal infection in this series having been demonstrated and welcomed, speculation arises as to why the protection is incomplete and what might be done to eliminate the failures. Keettel, Scott, and Plass suggested the presence of penicillin-resistant bacteria, mutation of the organisms, or inadequate dosage as possible causes of nonsuccess. If the first or the second were determined to be factors, it would appear reasonable to add such other antibiotics as would be found necessary to eliminate the offenders. However, the fact that puerperal infection (when it did occur in our series) usually responded within a week to treatment which included peni-

cillin, strongly suggests that the first two possibilities are of no great importance and that the bacteria for the most part were not resistant to penicillin.

In favor of the third possibility, Keettel, Scott, and Plass found that increasing the initial dose of penicillin reduced the occurrence of two-day-or-more infection to less than one-half (from 6.9 to 3.0 per cent). Although their series is not comparable to the one from Herman Kiefer Hospital since they had a total of only 26 instances of prolonged labor as opposed to 200 infection-prone cases in our group, there are some data regarding the latter which support the larger dosage idea. For example, the patients without penicillin prophylaxis in labor showed the expected tendency toward increased puerperal infection with the longer labors, with the greater length of time before delivery after premature rupture of the membranes, or both. When the lapse of time was 20 but less than 40 hours, puerperal infection occurred in 6.2 per cent; if 40 but less than 60 hours, it was 4.8 per cent; and 60 or more hours, the incidence was 12.9 per cent. On the other hand, in the treated group the tendency was the reverse, the percentages being 16.7, 7.7, and 5.3. The probable explanation for this difference is obviously the conclusion that the longer the lapse of time, the larger number of doses and increased total of penicillin given. As a caution, though, it should be stated that there were frequent failures of antepartum fever to subside during labor in spite of heavy penicillin treatment. This indicates the possibility of inaccessibility of the bacteria to the therapy during labor. Moreover, there were a substantial number of instances of puerperal infection in both our series and that of Keettel, Scott, and Plass. In our series, some of these followed very large total amounts of prophylactic penicillin. A few of our patients were seriously ill, and we also know of at least one patient who reportedly died of streptococcic peritonitis after prolonged labor in spite of energetic penicillin treatment both before and after delivery. The evidence, then, indicates a considerable and welcome prophylactic effect of penicillin given during labor to infection-prone patients. However, the protection is far from complete, and meticulous attention to aseptic technique and the favorable condition of the patient are still of profound importance. For the same reasons, although more frequent delivery by cesarean section in these patients appears justified and feasible, evidence at present indicates that extension of its use should be undertaken cautiously.

Fetal Results

The effect of penicillin during labor on fetal infection is as yet almost entirely conjectural. As stated before, Keettel, Scott, and Plass suggested the possibility of fetal protection from infection due to the presence of therapeutic levels of penicillin in the amniotic fluid, though this was not demonstrated by their data. In the small series reported by Woltz and Stashak there were two fetal deaths before delivery. The heart blood of the one whose mother received prophylactic penicillin gave a negative culture, whereas the other from an untreated mother was positive. A third baby died of pneumonia after delivery, the mother having received penicillin during labor.

In the Herman Kiefer series, the gross mortality figures indicate no advantage to the fetus in the prophylactic use of penicillin. There were 14 deaths before and after delivery among the 103 (twins 3 times) babies born of mothers who received no penicillin in labor; and of the 101 (twins once) whose mothers were treated prophylactically in labor there were 18 who died. An analysis of the cases failed to change this impression. Of the 14 lost babies born of mothers without penicillin there were 7 who died of extreme prematurity, birth injuries, prolapsed umbilical cord, or developmental anomalies incompatible with survival—leaving 7 in whom infection might possibly have

been a cause of, or at least a factor contributing to, the death. The same figures for the prophylactically treated group were 6 and 12, respectively. Moreover, of the 7 possibly infected babies in the first or untreated group, 6 were dead before admission and only one died while under observation. In the second group, or the one with penicillin, 6 patients also entered the hospital with the fetal heartbeat absent; but, in contrast to the single instance in the first group, there were 5 babies who died in labor after penicillin was started, and a sixth gave evidence of fetal distress before delivery and could not be resuscitated following birth. While it is not certain that these 6 babies all died of infection, it does seem significant that in every instance there was inflammation of the placenta, and in 5 of the 6 antepartum fever was present. It could well be that this poor showing for babies born of mothers receiving penicillin in labor was in some part due to the generally more serious cases included in this group, as mentioned before. Obviously, though, and contrary to the maternal results, the actual figures in this experiment offer no statistical support for the suggested possibility that the intrauterine child can be protected by prophylactic penicillin given the mother during labor.

TABLE V. BABIES LOST TO 100 MOTHERS WITH PROPHYLACTIC PENICILLIN DURING LABOR AND 100 WITHOUT PENICILLIN

	TOTAL BABIES	GROSS FETAL LOSS	LOST DUE TO ACCI- DENTS OF LABOR, BIRTH INJURY, PRE- MATURITY, ANOMA- LIES, ETC.	STILLBORN, DEAD ON ADMISSION	STILLBORN, ALIVE ON ADMISSION
With penicillin	101	18	6	6	6
No penicillin	103	14	7	6	1

Summary

Although penicillin given during labor should theoretically give protection against infection, there are as yet only a few reports which present reliable data indicating actual results. In the present experiment 100 obstetrical patients with premature rupture of the membranes for at least 20 hours, labor for 20 hours or more, or both were given prophylactic penicillin at regular intervals before delivery; whereas a like number of controls were untreated. Taking into account the differences in the two groups (as shown by comparisons of the length of labor, lapse of time after premature rupture of the membranes, incidence of antepartum fever, inflammation of the placenta, etc.) there was demonstrated a considerable protection against puerperal infection in such patients from the use of penicillin during labor. However, welcome as is this protection, the prevention was so far from complete in these infection-prone patients as to suggest only a very cautious extension of the indications for delivery by cesarean section in such difficult cases. In agreement with Keettel, Scott, and Plass, there was some reason to believe that the use of larger prophylactic doses of penicillin should be expected further to reduce the occurrence of puerperal infection.

On theoretical grounds it has been suggested that the fetus should receive some protection against antenatal infection from the penicillin given to the mother before delivery, though factual evidence regarding this seems to be largely lacking. In the present series the gross results, as well as an

analysis of the figures, failed to indicate any advantage to the child from prophylactic antepartum treatment of the mother.

Grateful acknowledgment is made to Parke, Davis & Company for the supplies of penicillin and to Dr. E. A. Sharpe of the same firm for the valuable advice required for the conduct of this experiment.

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955 FISHER BUILDING

THE TREATMENT OF IRON DEFICIENCY ANEMIA OF PREGNANCY WITH INTRAVENOUS IRON*

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IN 1947 Nissim¹ reported the successful intravenous administration of a stable solution of saccharated oxide of iron. Previously, Cappell² in 1930 showed that iron could be given intravenously; but several workers,^{3, 4} after careful investigation, concluded that, while the therapeutic response to intravenous iron was marked, and while it was utilized almost 100 per cent by the body for the production of hemoglobin, the reactions were sufficiently severe as to contraindicate its use. However, following Nissim's report, other workers,^{5, 6, 7} using an improved preparation of saccharated oxide of iron, reported favorable results with minimal toxic reactions. These more recent favorable reports indicate the necessity for additional clinical evaluation.

Iron deficiency anemia has always plagued the obstetrician. It is a well-established fact that in normal pregnancy there is a gradual decrease from the nonpregnant state in the volume of packed red blood cells, red blood count, serum iron, and hemoglobin.⁸ Values reach their lowest levels just prior to term and rapidly return to normal during the first few weeks of the puerperium. These changes have been thought due to the increase of the plasma volume beginning at the twenty-fourth to twenty-eighth week of gestation and reaching its peak at the thirty-sixth week.^{9, 10} However, there is a significant number of women in whom the hemoglobin level, serum iron value, and volume of packed red blood cells decrease beyond the physiological level and in whom a pathological anemia develops. A small number of these anemias are macrocytic or have other etiological factors, but by far the majority are microcytic, hypochromic, and due to iron deficiency.¹¹ It is in this latter type that intravenous iron may be of value.

Material and Methods

Twenty-six patients were followed in this study. Nine were definitely anemic with hemoglobin varying from 5.4 to 10 Gm. per 100 c.c. of whole blood. All of these patients manifested the usual complaints, varying with the severity of the anemia. Eight patients with hemoglobin values of 10.5 Gm. were placed in a mildly anemic group. Nine normal patients were subjected to the medication in the second or early in the third trimester. They had no complaints, pregnancy was progressing normally, hemoglobins were within normal limits and varied from 11 to 12 Gm. They were studied for purposes of comparison with the other two groups.

Preliminary studies included the volume of packed red blood cells, red blood count, hemoglobin, and serum iron determinations. When these studies did

*The material used in this study was Feojectin, supplied by Smith, Kline & French Laboratories, Philadelphia, Pa.

not substantiate the diagnosis of iron deficiency, the case was not included in the series. The serum iron determinations were made using the Barkan-Walker method¹² and hemoglobin levels were determined by the Sahli-Adams acid hematin procedure. All laboratory work was done by the same technicians in order to reduce errors to a minimum and to make follow-up determinations comparable.

The total amount of intravenous iron given each patient was calculated according to the hemoglobin deficit. Fifteen grams of hemoglobin per 100 c.c. of whole blood and a total blood volume of 5,000 c.c. were considered normal. One gram of hemoglobin contains 0.0034 Gm. of elemental iron. Using this information, the exact amount of hemoglobin and the total iron deficiency present in each patient were calculated. For practical purposes, the calculations were simplified by multiplying the hemoglobin deficit by 50 to determine the total hemoglobin deficiency. This factor was multiplied by 0.0034 to determine the total elemental iron deficiency.

Goetsch⁴ reported that 71.8 to 99.7 (average 80.8) per cent of iron injected intravenously was utilized in the production of hemoglobin. Heath³ reported an average of 96 per cent, and other workers^{13, 14, 15} have confirmed the observation that parenterally administered iron is retained by the body and is quantitatively converted into hemoglobin. However, a low hemoglobin, particularly one that has developed over a long period of time and is due to iron deficiency, indicates a depletion of the iron stores in the body. This must be considered in calculating the amount of iron to administer. In this study, in order to replenish these iron stores, the deficiency as determined by calculation from the hemoglobin was doubled.

In previous reports, the methods of injecting the solution have varied. Some have advocated diluting the intravenous iron solution in normal saline, others in 5 per cent glucose solution. Our experience indicates that when so diluted, particularly in the higher doses, the frequency and severity of the toxic reactions increase. After trying various methods, it was found best to draw back on the plunger and dilute the iron preparation from two to four times in the patient's own blood, and to inject the solution slowly in from two to five minutes.

No definite schedule for administration of the medication was adhered to. Previous reports^{5, 6, 7} suggested a small test dose with gradual increases daily up to 100 mg., then 100 mg. daily or every other day until the total calculated dose had been given. This was done in the first few cases, but it was soon found that 100 mg. produced no more toxic reactions than smaller doses. In the majority of cases, 100 mg. were injected as the test dose. Daily thereafter, the amount given was increased by 100 mg. until the total calculated dose had been given, or until toxic reactions occurred. Seventy-nine per cent of the injections contained from 100 to 300 mg. of iron, 6 per cent under 100 mg., and 15 per cent, 400 to 500 mg. Most patients received the total calculated dose within three weeks' time.

In following the patients, hemoglobin, volume of packed red blood cells, red blood count, reticulocyte count, and serum iron determinations were made weekly. If the patients were in the second or early part of the third trimester, determinations were made less often.

Results

Evaluation of the results shows definite increase in hemoglobin in every patient. This increase was greater and occurred more rapidly than would be expected from iron orally administered. Neary¹⁶ reported 2.1 Gm. hemoglobin increase per 100 c.c. of whole blood in 6.9 weeks of oral therapy. Dieckmann,¹⁷

using oral iron-molybdenum complex, reported an increase of 1.73 Gm. in 4 weeks and 2 to 3.6 Gm. increase in 6 weeks. In the present study, both anemic and mildly anemic groups had an average hemoglobin increase of 1 Gm. per 100 c.c. whole blood in one week and 2 Gm. in 2 weeks. The time between the onset of therapy and delivery in the anemic group averaged 3.7 weeks and the mean total hemoglobin increase per 100 c.c. of whole blood in this time was 2.8 Gm. Two patients in the anemic group did not deliver until 4 and 6 weeks after receiving intravenous iron, and the mean hemoglobin increase in these two patients was 4.05 Gm. While the last figure is impressive and indicates a much greater increase than is usually obtained when iron is given by mouth, it represents only two patients. It is also true that occasional patients treated by oral iron will show such marked improvement. The significant finding is the rapidity with which hemoglobin was formed. The mildly anemic patients averaged a total increase of 2.0 Gm. hemoglobin per 100 c.c. of whole blood from the onset of therapy until delivery, while the nonanemic patients averaged but 1.8 Gm. increase during this time. This is as expected, since the higher the hemoglobin at the beginning of therapy, the smaller is the possible increment.

Table I shows the mean total gain in hemoglobin for each group studied. It also shows the changes that occurred in the volume of packed red blood cells.

TABLE I. MEAN HEMOGLOBIN AND VOLUME OF PACKED RED BLOOD CELLS IN PATIENTS RECEIVING INTRAVENOUS SACCHARATED OXIDE OF IRON

	INITIAL HGB.	HGB. AT TERM	INCREASE IN HGB.	INITIAL VPRBC	FINAL VPRBC	INCREASE IN VPRBC
Anemic	8.8	11.6	2.8	28.9	35.1	6.2
Mildly anemic	10.5	12.5	2.0	34.0	37.0	3.0
Nonanemic	11.8	13.6	1.8	36.1	41.1	5.0

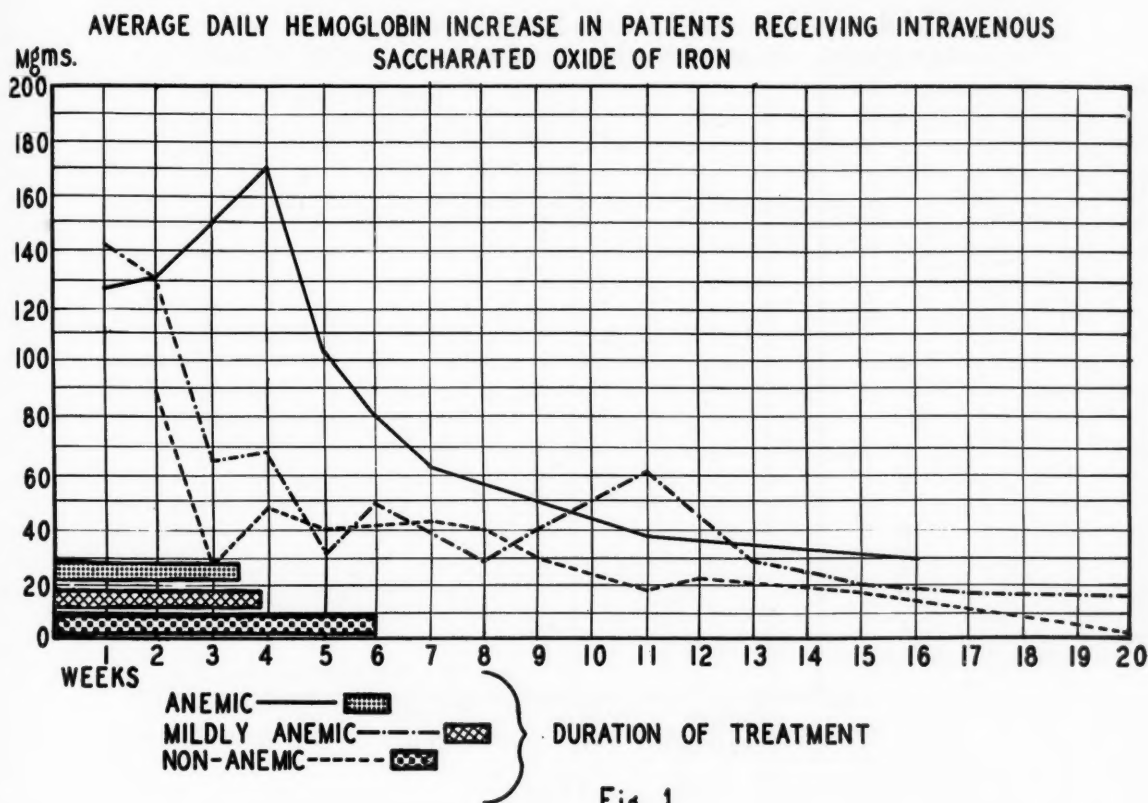
Anemic and mildly anemic patients had a total mean increase of 2.4 Gm. per 100 c.c. of whole blood. As expected, the lower the initial hemoglobin, the greater the total increase.

The changes in the volume of packed red blood cells coincide with the increase in hemoglobin. A mean increase in volume of packed red blood cells of 6.2 mm. occurred in the anemic group, while mildly anemic patients had a mean increase of 3.0 mm. The nonanemic patients, while the rate of hemoglobin increase was not remarkable, showed a total increase in hemoglobin rather than the expected drop. The mean volume of packed red blood cells at term was 41.1 mm. rather than the lower 37.9 mm. value in normal pregnancy reported by Fay and Cartwright.⁸ In other words, the physiological anemia of pregnancy previously thought to be due to hydremia occurring in the last trimester was eliminated. This finding suggests that the so-called physiological anemia in reality is an iron deficiency anemia. Further study of this point is indicated.

The efficacy of iron therapy in the treatment of iron deficiency anemia can be evaluated by determining the rate of daily hemoglobin increase. Heath¹⁸ states that iron therapy is adequate if the daily hemoglobin increment is 1 per cent per day (0.150 Gm.). Other investigators report daily hemoglobin increments up to 0.160 Gm. per 100 c.c. when iron is given by mouth. In this study, the mean daily hemoglobin increment in the anemic patient was 0.129 Gm. in the first week, with increasing values reaching a peak of 0.171 the fourth week, and then rapidly dropping to below 0.100 Gm. daily. The significant finding here is the rapidity of response in the first days of treatment.

It has been shown that iron introduced intravenously into the body is almost entirely retained. Kuhns¹⁹ found a total of only 0.89 per cent in the urine after large doses of intravenous iron had been given to patients with iron deficiency anemia. It has been stated that the retained iron is used quantitatively

in the production of hemoglobin. Since 1 Gm. of hemoglobin contains 0.0034 Gm. of iron, theoretically, 1 Gm. of intravenous iron should produce a total of 294 Gm. of hemoglobin or 5.9 Gm. per 100 c.c. whole blood. In this study, 1 Gm. of iron produced a mean of only 1.7 Gm. of hemoglobin per 100 c.c. of whole blood. The iron not evident as hemoglobin probably was used to replenish the lowered iron stores in the liver, spleen, and bone marrow. In every patient in this study, the hemoglobin continued to increase following delivery. These increments were not included in the study because hemoglobin values usually increase post partum as plasma volume decreases. However, rapid hemoglobin regeneration is not apparent even with the decrease in hydremia unless iron is available from the storage areas. This study indicates that these stores are well filled by the iron given intravenously.



Serum iron determinations are also of interest. The present knowledge of iron physiology indicates that iron exists in three states in the body from point of view of their relations to circulating hemoglobin—the iron of hemoglobin, approximately 55 per cent; iron reserve stores mainly in the liver, spleen, and bone marrow, 30 to 37 per cent; and the tissue iron which is unavailable for blood formation. Iron is transported in the body as plasma iron which remains in equilibrium with iron storage depots and with iron being diverted to bone marrow for hemoglobin synthesis. Low values in iron deficiency anemia indicate depletion of body stores and active erythropoiesis. Normal values in nonpregnant women vary but are reported by Fay and Cartwright⁸ to be 105 ± 5.5 gamma per cent. In normal pregnancy, this value gradually decreases from about the twentieth week and at term is 59 ± 6.4 gamma per cent. This low value indicates a decrease in the storage iron in the body.

In this study, the mean serum iron value before therapy in the anemic patients was 55 gamma per cent. Following therapy, the greatest mean increase was 261 gamma per cent and the value gradually decreased to 156 gamma per cent at term. The values for the mildly anemic patients and the nonanemic patients followed the same trend, but with smaller mean increases. In all three groups, the serum iron leveled off to normal values of 70 to 120 gamma per cent by the sixth to eighth week post partum. Fig. 2 graphically shows these values.

The important finding is the comparison between the mean serum iron values in the anemic groups at term and the 59 ± 6.4 gamma per cent value considered normal in the nonanemic patient. It appears that intravenous iron not only rapidly corrected the anemia, but also replenished completely the reserve iron stores in the body.

MEAN SERUM IRON DETERMINATIONS IN PATIENTS RECEIVING INTRAVENOUS SACCHARATED OXIDE OF IRON

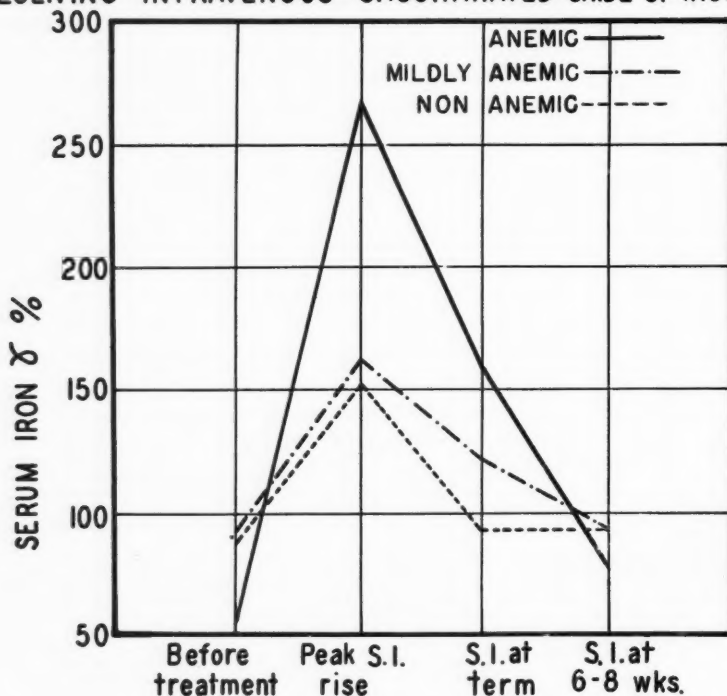


Fig. 2.

This study of the daily rate of hemoglobin increase, total hemoglobin increase, volume of packed red blood cells, and serum iron values indicates that intravenous iron, when used to treat iron deficiency anemia of pregnancy, corrects the anemia more rapidly and more completely restores the iron reserves of the body than iron by mouth.

Three typical cases are represented in Fig. 3.

Toxic Reactions

All investigators report varying degrees of toxicity to intravenous iron medication. Prior to Nissim's report in 1947, they were almost unanimous in the opinion that the disadvantages of toxicity reactions outweighed the advantages. Careful evaluation of this aspect of the problem is important.

One hundred ninety-three injections were made during this study. The amount of iron in each injection varied from less than 100 mg. to 500 mg. One patient received 1 Gm. With each injection, the patient was carefully studied and unpleasant symptoms elicited. As has been noted by other investigators, the following symptoms were encountered: suffusion, light-headedness, dizziness, pain in the arm and shoulder and along the course of the vein in which the injection was being made, nausea, cough, sacral backache and pain radiating down the posterior aspect of the legs, pain in the knee, vomiting, thrombophlebitis, and shock. Occasionally a patient would complain of a vague generalized discomfort difficult to describe. These reactions were classified as mild, moderately severe, and severe, and approximate those reported by Kuhns.¹⁹

GRAPHIC SUMMARY OF TYPICAL CASES RECEIVING INTRAVENOUS SACCHARATED OXIDE OF IRON

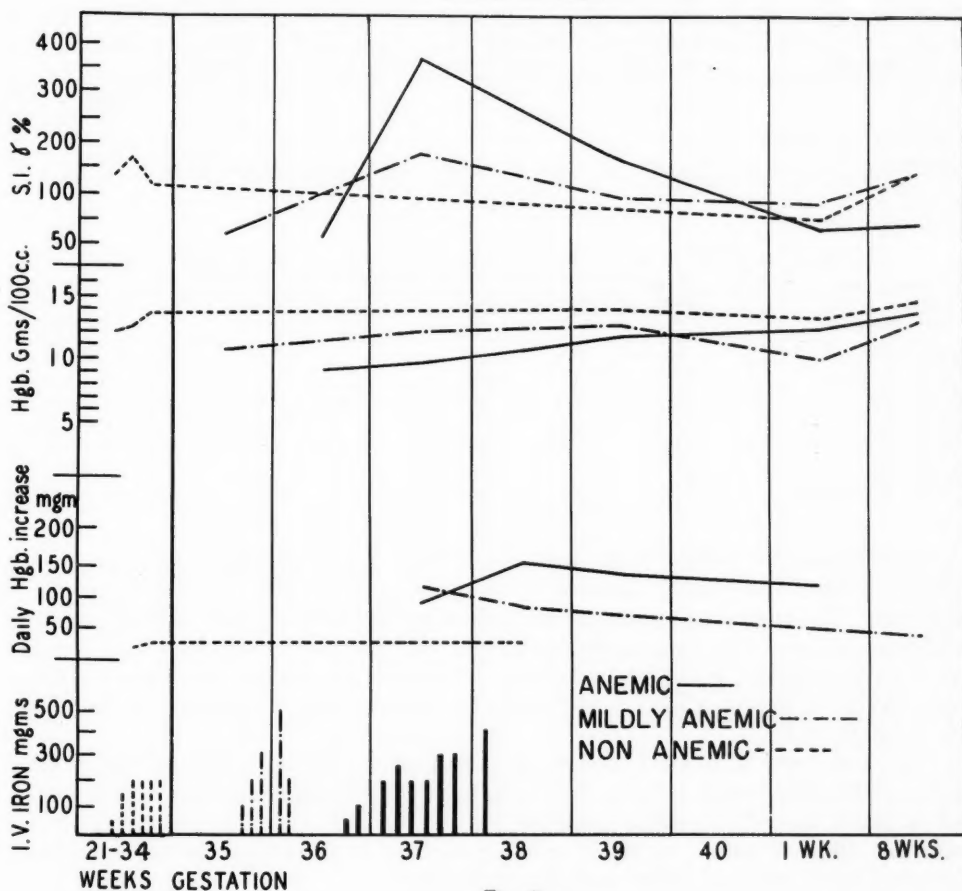


Fig. 3

The mild reactions were transient and consisted of suffusion, weakness, light-headedness, minimal pain, cough, and backache. When these symptoms were more severe and persisted up to five minutes or were accompanied by dyspnea, dizziness, pain along the course of the vein, or vomiting, they were classified as moderately severe. When they lasted more than five minutes or when shocklike state occurred, reactions were classified as severe. Severe reactions occurred but four times, and with doses of 400 and 500 mg. and 1 Gm.

The iron solution is extremely irritating to the tissues and cannot be tolerated outside the vein. On several occasions, a slight amount was inadvertently injected subcutaneously and intense pain indicated the fact before more than a few millimeters of the material were injected. No sloughing occurred in these cases. One patient developed severe thrombophlebitis following a prolonged injection with the material diluted in normal saline. As indicated previously, the best method of injection was to dilute the material in the patient's own blood. After this procedure was adopted, vein irritation rarely occurred, and then with large doses or too rapid injection. Tables II and III summarize the toxic reactions.

TABLE II. TOXIC REACTIONS TO INTRAVENOUS SACCHARATED OXIDE OF IRON THERAPY

REACTION	NO. OF INJECTIONS			PER CENT OF TOTAL INJECTIONS	SIZE OF DOSE (GM.)
	DIL. IN NORMAL SALINE SOLUTION	DIL. IN BLOOD	TOTAL		
None	47	78	125	65	0.025 to 0.500
Mild	27	25	52	27	0.025 to 0.500
Moderately severe	8	4	12	6	0.050 to 0.500
Severe	1	3	4	2	0.400 to 1.000
Total	83	110	193	100	

TABLE III. TOXIC REACTIONS TO INTRAVENOUS SACCHARATED OXIDE OF IRON

DOSE	NONE %	MILD %	MODERATE %	SEVERE
1.000 Gm.	0.0	0.0	0.0	1 patient
0.500 Gm.	33.0	40.0	13.5	13.5%
0.400 Gm.	57.0	36.0	0.0	7.0
0.300 Gm.	69.0	21.0	10.0	0.0
0.200 Gm.	63.0	33.0	4.0	0.0
0.100 Gm.	78.0	18.0	4.0	0.0
Under 0.100 Gm.	64.0	18.0	18.0	0.0

Sixty-five per cent of all injections were given without reactions of any kind, and in 27 per cent reactions were so mild and transient as to be of no consequence. Ninety-two per cent of the 193 injections were given without difficulty. Although some individual variations occurred, in general, as the dose increased, the severity of the reaction increased. Table III indicates that up to 300 mg. were given safely without materially increasing the frequency or severity of the toxic reactions.

As has been indicated, fewer reactions occurred with the material diluted in the patient's blood. Forty-three per cent of all injections were given diluted 1:4 or more in normal saline, and 53 per cent of all reactions occurred when the iron was thus diluted. Sixty-seven per cent of the moderately severe reactions occurred when normal saline solution was used.

Comment

Whether or not there is a need for parenteral iron in the treatment of iron deficiency may be debated. Wintrobe²¹ states that there are few patients with iron deficiency anemia who will not respond to oral iron. In those cases in which evidence of gastrointestinal irritation develops, iron can be tolerated if small doses are given initially and the quantity increased gradually.

However, the pregnant woman with iron deficiency anemia often becomes a unique problem. If the general iron deficiency state is perceived sufficiently

early in her pregnancy, therapy by mouth is adequate. This is true even though only a small percentage of the iron ingested (3.1 per cent in uncomplicated hypochromic anemia) is absorbed through the intestinal mucosa and four to six weeks are required for maximum hemoglobin production by the body. However, several conditions often occur in conjunction with pregnancy which preclude this maximum response to oral iron. Many patients are seen for the first time late in the last trimester and there is insufficient time for response to oral iron therapy. In the past, in these cases whole blood transfusions have been given. Many pregnant patients, because of nausea and vomiting, cannot ingest iron by mouth. Achlorhydria which sometimes accompanies pregnancy interferes with absorption of orally ingested iron. Rarely one has to treat hypochromic microcytic anemia of pregnancy in which the etiological factor cannot be determined and which does not respond to oral therapy. Finally, the fetal requirement for iron which is at its peak during the last trimester also contributes to the lowered hemoglobin content of the mother's blood. Ordinarily this demand is not sufficiently great to produce anemia, but if the iron reserves are low, it will add to the factors producing iron deficiency anemia in the pregnant woman.

TABLE IV. SUMMARY OF MORPHOLOGICAL AND CHEMICAL STUDIES ON 26 PATIENTS RECEIVING INTRAVENOUS SACCHARATED OXIDE OF IRON

PATIENT	AGE	WEEK OF GESTATION	VPRC	HGB.	MCV*	MCHC*	SERUM IRON GAMMA PER CENT	TOTAL IRON GIVEN (GM.)	HGB. AT DELIV.	DAYS OF THERAPY
<i>Anemic.—</i>										
V. M. P.	25	31	22	5.4	72.8	24.5	65	3.200	10.5	64
R. S.	27	36	27	8.5	68.0	32.0	51	2.200	12.0	24
V. R.	28	30	27	8.5	80.8	31.4	40	1.600	11.5	6
M. S.	26	39	27	8.5	75.0	32.0	63	2.200	9.5	16
V. P.	42	36	35	9.0	78.6	26.0	55	2.000	11.5	17
A. L.	21	36	29	9.0	74.0	33.0	23	1.900	13.0	26
C. F.	19	30	30	10.0	75.0	33.0	45	1.400	11.5	14
B. C.	18	22	31	10.0	76.5	32.2	93	1.400	13.0	48
Z. D.	31	36	33	10.0	79.5	31.8	64	1.700	12.0	17
Mean	—	—	29	8.8	75.6	30.1	55	—	11.6	26
<i>Mildly Anemic.—</i>										
B. G.	31	36	36	10.5	88.0	29.0	96	1.500	13.5	35
B. H.	33	38	33	10.5	89.0	32.0	63	1.400	12.0	11
J. L.	19	38	34	10.5	84.0	31.0	76	1.450	12.0	11
R. G.	17	35	34	10.5	79.6	30.8	56	1.500	12.5	25
M. M.	19	24	35	10.5	74.0	30.0	142	1.530	13.0	100
N. U.	17	30	32	10.5	85.2	32.8	34	1.600	11.5	28
V. T.	17	17	35	10.5	76.5	30.0	94	1.535	12.5	157
S. G.	32	19	33	10.5	78.2	32.2	162	1.530	13.0	133
Mean	—	—	34	10.5	81.8	30.9	90	—	12.5	—
<i>Nonanemic.—</i>										
M. P.	24	29	33	11.0	71.5	33.3	104	1.350	14.0	84
G. K.	19	36	34	11.0	80.5	32.4	31	1.500	13.0	21
I. K.	28	24	35	11.5	83.0	33.0	60	1.180	13.5	92
A. M.	23	33	35	11.5	87.0	33.0	73	1.250	13.5	49
M. C.	21	31	39	12.0	78.0	31.2	79	0.950	14.0	67
B. B.	34	22	36	12.0	82.0	33.8	132	1.080	14.0	114
I. M.	20	29	37	12.0	88.0	32.4	53	1.100	14.0	92
A. R.	33	19	39	12.5	85.5	32.0	132	0.800	14.0	153
S. G.	23	30	37	12.5	80.8	33.6	109	0.925	12.5	87
Mean	—	—	36	11.8	82.9	32.7	86	—	13.6	—

*MCV = corpuscular volume.

MCHC = corpuscular hemoglobin concentration.

This study indicates that when any of these conditions exist, a preparation of iron suitable for intravenous use is now available.

Summary

1. Twenty-six patients were treated with intravenous saccharated oxide of iron. Nine had iron deficiency anemia with hemoglobins varying from 5.4 to 10 Gm. per 100 c.c. of whole blood. Eight patients had hemoglobins of 10.5 Gm. Nine patients had normal hemoglobin.

2. Results indicate that in iron deficiency anemia of pregnancy, intravenous iron produces a greater total and a more rapid increase in hemoglobin than oral iron. The average increase in these patients was 1 Gm. hemoglobin per 100 c.c. of whole blood in one week, and 2 Gm. in two weeks, and as high as 4.05 Gm. in 4 to 6 weeks. The volume of packed red blood cells and serum iron levels substantiate these findings.

3. Toxic reactions were significant. Doses varied from less than 100 mg. to as high as 1 Gm. of intravenous iron. Sixty-five per cent resulted in no reactions, 27 per cent mild, 6 per cent moderately severe, and 2 per cent severe. Most frequent reactions were light-headedness, suffusion, weakness, nausea, venospasm, headache, sacral backache. Thrombophlebitis and shocklike state occurred twice, both times with large doses.

4. Following a test dose of 100 mg., up to 300 mg. of intravenous saccharated oxide of iron can be given daily without materially increasing toxic reactions. Doses of 100 to 200 mg. are recommended.

5. The best method of injection is to dilute the saccharated oxide of iron solution in the patient's own blood. Injection should be done slowly and care taken to avoid subcutaneous injection of the material.

6. Intravenous saccharated oxide of iron for the treatment of iron deficiency anemia of pregnancy is effective in those patients who cannot tolerate iron by mouth, who have excessive nausea and vomiting of pregnancy, who have failure of absorption of iron from the gastrointestinal tract, and who present themselves late in pregnancy with an existing anemia and insufficient time for response to oral therapy.

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CESAREAN SECTION AFTER PROLONGED LABOR. INFLUENCE OF PROPHYLACTIC SULFONAMIDE AND PENICILLIN THERAPY ON OPERATIVE PROCEDURE AND END RESULTS*

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ONE of the more important advances in the field of obstetrics has been the attainment of an increasing safety in the performance and results of the cesarean section operation. With the betterment of surgical and anesthetic techniques, the more ready availability and safer administration of blood, and the introduction of the antibacterial drugs, the operation no longer carries the danger of death and morbidity from severe infection and hemorrhage.

The present controversy concerns the most preferable type of abdominal operation to be done in cases with potential or overt infection. The most extreme point of view expressed by Dieckmann¹ maintains that in all such infected cases, the entire uterus and cervix must be removed for best results. The extraperitoneal types of operation are still supported by Cosgrove, Waters, and Barrett² as the safest treatment in such cases. However, several recent reports from the Sloane Hospital for Women,³ the New York Hospital,⁴ and the Milwaukee Hospital⁵ express a trend toward the wider acceptance of the lower segment transperitoneal cesarean section with appropriate adjuvant therapy.

The variation of viewpoint is of especial interest to us on the obstetrical service at Bellevue Hospital, where, since June 1, 1940, the policy has been to employ the low flap cesarean section as the procedure of choice for abdominal delivery, particularly if the patient is in labor. Prior to this period the indications for the extraperitoneal approach were regarded as very limited and only encountered on rare occasions. As the sulfonamides and the antibiotics were introduced, they were liberally employed prophylactically in the management of cases treated by cesarean section.

In an attempt to evaluate fully what our results with this type of operation have been, particularly with the use of the sulfonamides and penicillin, a group of cases offering the greatest hazards especially from the point of view of infection have been analyzed in the body of this paper.

Material

From June 2, 1940, to Dec. 31, 1949, there were 500 cesarean sections performed on the obstetrical service at Bellevue Hospital, an incidence of 2.7 per cent. There were no deaths due to hemorrhage or infection in these 500 cases.

*Presented before the Tri-city Meeting of the New York, Philadelphia, and Boston Obstetrical Societies, April 12, 1949, and the Queen's County Medical Society, May 19, 1950.

The single mortality occurred in 1942 in a patient with pre-eclampsia, fibroids, and placenta previa delivered by elective operation. She died on the fifth day after operation under puzzling circumstances. An autopsy did not clarify the cause of death but revealed no evidence of infection.

Seventy (14 per cent) of these cesarean sections were performed on patients who had been subjected to a labor of thirty hours or more. Sixty-nine of these were delivered by low flap cesarean section and one by a Latzko extraperitoneal type. This latter operation was performed in November, 1941; since then no extraperitoneal sections have been done on this service.

On December 31, 1941, the first patient was treated with sulfanilamide locally at operation as a prophylaxis against infection. From that time, up to March, 1948, when this procedure was discontinued, there were thirty-one additional cases treated in this manner. Sulfanilamide (in one case sulfathiazole) varying in amounts from 5 to 15 Gm. was placed in the operative field—under the bladder flap, in the uterovesical pouch of peritoneum, in the wound, and occasionally in the uterus.

On Oct. 5, 1944, the first patient was treated with penicillin postoperatively as a prophylactic measure. Since then, penicillin has been used prophylactically beginning within the first several hours to forty-eight hours after section in forty-three cases.

On April 4, 1945, penicillin was first used prophylactically in labor. Since then there have been thirty-five cases treated in this manner. From December, 1945, every case with prolonged labor delivered by cesarean section has received penicillin prophylactically with or without the use of the sulfonamides.

TABLE I. CASES WITH PROLONGED LABOR AND DELIVERY BY CESAREAN SECTION

Group A—Patients not receiving sulfonamides or penicillin at any time	9
1940-1942	6
1945	3
Group B—Patients receiving sulfonamides locally at operation	32
Group C—Patients not receiving sulfonamides locally at operation, but receiving sulfonamides or penicillin before or after operation	29
Total	70

TABLE II. ANALYSIS OF GROUP B, PATIENTS RECEIVING SULFONAMIDES LOCALLY AT OPERATION

Patients receiving sulfonamides only at operation	10
Patients receiving additional sulfonamides for postoperative complications	4
Patients also receiving penicillin with or without additional sulfonamides	18
Total	32

TABLE II, A. ANALYSIS OF PATIENTS RECEIVING SULFONAMIDES LOCALLY AT OPERATION, AND PENICILLIN, WITH OR WITHOUT ADDITIONAL SULFONAMIDES

Penicillin in labor and post partum prophylactically	4
With sulfonamides prophylactically postop.	3
With sulfonamides for postop. complications	5
Penicillin post partum prophylactically	1
With sulfonamides prophylactically postop.	2
With penicillin locally at operation and sulfonamides for postop. complications	1
With sulfonamides for postop. complications	1
With streptomycin (for the peritonitis)	1
Total	18

At present the prophylactic use of penicillin carried on through the operation and the early days of the postoperative period is the routine therapy.

Inasmuch as the period from 1940 to 1949 covers the time of changing modes of therapy with the sulfonamides and penicillin, it is not surprising to find quite a variation in the usage of these drugs in these cases. The accent was on the use of the sulfonamides first, then came the transition stage as penicillin was introduced, and finally the emphasis drifted to the use of penicillin. Tables I through III present the classification of these cases based on the mode of treatment with the sulfonamides and penicillin.

TABLE III. ANALYSIS OF GROUP C, PATIENTS NOT RECEIVING SULFONAMIDES LOCALLY AT OPERATION, BUT RECEIVING SULFONAMIDES OR PENICILLIN BEFORE OR AFTER OPERATION

Sulfonamides only for postoperative complications	3
Penicillin with or without sulfonamides	26
Prophylactic penicillin post partum only	1
With sulfonamides for postop. complications	1
Prophylactic penicillin in labor and post partum	11
With sulfonamides prophylactically postop.	6
With sulfonamides in labor and prophylactically postop.	1
With sulfonamides for postop. complications	5
With aureomycin prophylactically postop.	1
Total	29

There were fifty-eight cases in this series in which the sulfonamides and penicillin were used at some time in labor, during operation, or postoperatively as a prophylactic measure against infection. One of these cases will be eliminated in the study of this particular group of cases because of its unusual nature. Tuberculous peritonitis was discovered at the time of operation. The patient received penicillin prophylactically following operation as well as streptomycin. She was eventually well enough to be transferred to a sanatorium on her thirty-ninth postoperative day.

The fifty-seven cases to be analyzed occurred from January, 1942, to Dec. 31, 1949. Table IV presents the manner in which prophylactic drugs were employed in this group.

TABLE IV. PATIENTS WITH PROLONGED LABOR RECEIVING EITHER SULFONAMIDES AND/OR PENICILLIN PROPHYLACTICALLY

Patients with sulfonamides used locally at operation, with or without additional sulfonamides and penicillin (Group B, excluding one case of the peritonitis)	31
Patients with sulfonamides not used at operation, with penicillin used prophylactically, with or without additional sulfonamides (major part of Group C)	26
Total	57

These cesarean sections were all done at term. The duration of the prolonged labors varied from 30 hours to 101 hours and 43 minutes (4 plus days), with the average duration of labor 47 hours and 31 minutes. All but three of these patients had ruptured membranes, the duration with ruptured membranes varying from 6 hours and 50 minutes to 185 hours and 50 minutes (approximately 9 days. The average duration of ruptured membranes was 39 hours and 33 minutes. Rectal and vaginal examinations in these complicated cases, were done without hesitation.

In the majority of cases, the indications for cesarean section were multiple, the prolonged duration of labor usually playing a part in the decision to terminate labor by section. These indications are classified into primary and

secondary groups, the primary indication being the principal cause for which the cesarean section was performed. The most frequent indication in twenty-eight cases (49.1 per cent) was cephalopelvic disproportion.

TABLE V. INDICATIONS FOR CESAREAN SECTION IN 57 CASES OF PROLONGED LABOR

<i>Primary Indications.—</i>	
Cephalopelvic disproportion	28
Prolonged labor with lack of progress (2 with breech presentation)	15
Abnormal positions of the vertex (1 persistent mentum posterior)	4
Uterine inertia (2 with breech presentation)	3
Cervical dystocia	3
Bandl's ring (1 with breech presentation)	2
Failure to engage after trial of labor (without evidence of cephalopelvic disproportion)	1
Breech presentation with contracted pelvis	1
Total	57

TABLE V, A. SECONDARY INDICATIONS

<i>In Addition to the Primary Indications Occurring in the Following Instances.—</i>	
Uterine inertia	25
Abnormal positions and presentations	12
6 extended vertex positions	
6 breech presentations	
Cervical dystocia	6
Failure to engage after trial of labor (without evidence of cephalopelvic disprop.)	6
Prolonged labor with lack of progress	5
Increasing tonicity of the uterus (without definite contraction ring)	3
Mild pre-eclampsia and hypertension	3
Soft tissue edema	1
Foreign body in bladder	1
Psychosis	1

As previously mentioned, fifty-four of the fifty-seven patients had ruptured membranes. In eighteen cases with ruptured membranes (31.5 per cent) there was some indication of an amniotic sac infection. In ten cases the only indication was a temperature elevation in labor above the previous norm with rises to 99.6° to 100.4° F., without any other explanation for the temperature elevation. In eight cases grossly purulent amniotic fluid was found at operation; in addition, temperature elevations in labor to 99.6°, 100.4°, 101°, and 101.2° F. were present in four cases.

TABLE VI. MORBIDITY INCIDENCE IN 57 CASES OF PROLONGED LABOR

Nonmorbidity	26 or 45.6%
Morbidity	31 or 54.4%
Total	57
100° Scale	31
100.4° Scale	24
101° Scale	17 or 30%

TABLE VII. INCIDENCE OF MORBIDITY BY YEARS

	TOTAL	MORBID	INCIDENCE
January, 1942-November, 1945 (Before routine use of penicillin)	20	12	60%
December, 1945-December, 1949 (After routine use of penicillin)	37	19	52%

No deaths occurred in this series. Therefore, the postoperative morbidity and complications remain the criteria for the judgment of the efficacy of the management. The morbidity for cesarean sections has been calculated on the basis of a temperature rise to 100° F. or over on two occasions, at least 24 hours apart, excluding the first 72 hours postoperatively. Tables VI through X present an analysis of the postoperative morbidity and complications. Table XI presents a detailed analysis of the eight cases in which grossly purulent amniotic fluid was found at the time of operation.

TABLE VIII. MORBIDITY IN RELATION TO DRUG THERAPY

	TOTAL	MORBID	INCIDENCE
Patients without prophylactic drug therapy (June, 1940-Nov., 1945)	12	9	75%
Patients with prophylactic drug therapy before routine use of penicillin (Jan., 1942-Nov., 1945)	20	12	60%
After routine use of penicillin (Dec., 1945-Dec., 1949)	37	19	52%

TABLE IX. PRINCIPAL CAUSES FOR MORBIDITY IN 31 CASES

Endometritis	28
Urinary tract infection	2
Wound infection	1
Total	31

TABLE X. ALL POSTOPERATIVE COMPLICATIONS IN 57 CASES

Endometritis	28
Moderate to marked distention	15
Anemia	13
Cyanosis due to sulfonamides (rec'd at operation)	7
Subinvolution of uterus	5
Urinary tract infection	4
Urinary retention (12 hrs., 48 hrs., 5 days)	3
Wound infection (one superficial)	2
Toxic psychosis (both recovered)	2
Retained secundines	1
Pneumonia	1
Hematoma of wound	1

Anemia as a postoperative complication occurred in thirteen cases (22.8 per cent). The criteria for anemia are based on blood counts, a red blood cell count of 3.5 million or lower and/or a hemoglobin of 75 per cent (10.5 Gm.) or lower.

The estimated blood loss associated with the operation varied from 100 to 900 c.c. A blood loss of 500 c.c. or over is considered a complicating hemorrhage. There were ten cases of hemorrhage at the time of operation, one of a delayed postoperative hemorrhage to a total amount of 900 c.c., an incidence of 17.5 per cent.

In twenty-nine cases transfusions were given either during operation or immediately following operation. One patient received 300 c.c. of blood, twenty-three received 500 c.c., four received 1,000 c.c., and one 1,500 c.c. Additional blood transfusions, usually for marked anemia, were given later in the postoperative course to four patients.

There was a definite trend toward the administration of more blood dating from November, 1946. Since that date, twenty-nine patients were delivered by

TABLE XI. EIGHT CASES OF PROLONGED LABOR WITH FINDING OF GROSSLY PURULENT AMNIOTIC FLUID AT OPERATION

PATIENT	DATE	DURATION OF LABOR	DURATION OF RUPTURED MEM.	SULFONAMIDES	PENICILLIN	MOREIDITY AND POSTOP. COMPLICATIONS
F. M. Para 0	JAN. 1945	59 hrs. 45 min.	34 hrs. 15 min.	Sulfadiazine in labor Sulfanilamide at op. Sulfadiazine p.o. 3-4, 8-15 days	At op. P.o. to 17th day 15,000 u. q 4 h.	101° scale Endometritis Slight distention Urinary retention for 48 hrs. Cyanosis due to sulfonamide
C. G. Para 0	APR. 1946	70 hrs. 8 min.	118 hrs. 8 min.	Sulfanilamide at op. Sulfadiazine p.o. to 2nd day	In labor 15,000 u. q 3 h. P.o. to 5th day 15,000 u. q 3 h.	100° scale Urinary retention to 5th day Endometritis Moderate distention Subinvolution uteri
J. R. Para 0	DEC. 1946	32 hrs. 11 min.	32 hrs. 26 min.	Sulfanilamide at op.	P.o. to 5th 50,000 u. q 3 h.	Nonmorbid Moderate distention
P. I. Para 0	MAY 1947	61 hrs. 6 min.	80 hrs. 6 min.	Sulfanilamide at op. Sulfathiazole p.o. 6-9 days	In labor 15,000 u. q 3 h. P.o. 100,000 u. q 3 h. to 6th day	100.4° scale Endometritis Cyanosis due to sulfonamide
A. W. Para 1	JUNE 1947	34 hrs. 23 min.	20 hrs. 53 min.	Sulfathiazole at op. Sulfadiazine p.o. 13-16 days	In labor 50,000 u. q 3 h. P.o. 50,000 q 3 h. to 9th day	100.4° scale Endometritis Marked distention
L. M. Para 0	FEB. 1949	31 hrs. 57 min.	17 hrs. 27 min.	None	In labor, 50,000 u. q 3 h. P.o. 100,000 u. q 3 h. to 5th day	Nonmorbid
Z. H. Para 0	AUG. 1949	32 hrs. 43 min.	31 hrs. 33 min.	None	In labor, 300,000 u. pro- caine penicillin q 12 h. P.o. 300,000 u. procaine pen. b.i.d. to 8th day P.o. aureomycin 250 mg. q 4 h. to 6th day	100° scale Endometritis Moderate distention
J. R. Para 0	DEC. 1949	41 hrs. 38 min.	12 hrs.	None	In labor procaine penicil- lin 300,000 u. o.d. P.o. 100,000 u. pen. q 3 h. to 6th day then 300,000 u. proc. pen. o.d. to 9th day	100° scale Endometritis

cesarean section in this series and only six did not receive blood at any time. It is of interest to note that the blood bank was established at Bellevue Hospital in 1939 and was running efficiently in 1940. However, probably more important than the ready availability of blood in creating this trend is the increased incidence of hemorrhages in the cases after November, 1946. Table XII presents an analysis of the anemia, blood loss, and blood administered, comparing the group before with that following November, 1946.

TABLE XII. ANEMIA, BLOOD LOSS, AND BLOOD TRANSFUSIONS IN 57 CASES OF PROLONGED LABOR WITH DELIVERY BY CESAREAN SECTION

	JAN., 1942 TO NOV., 1946	NOV., 1946 TO DEC., 1949	TOTAL SERIES
Number of cases	28	29	57
Patients with anemia post partum	7 (25.0%)	6 (20.1%)	13 (22.8%)
Patients with hemorrhage	1 (3.6%)	9 (31.8%)	10 (17.5%)
Patients with blood at operation or immediately postop.	6 (21.4%)	23 (79.3%)	29 (50.9%)
Patients with blood later postop.	2 (7.1%)	2 (6.9%)	4 (7.0%)
Total blood given	8,250 c.c.	15,450 c.c.	23,700 c.c.
Average blood loss	293 c.c.	410 c.c.	353 c.c.

There were three fetal or neonatal deaths in this series of fifty-seven cases, an uncorrected fetal mortality incidence of 5.5 per cent. The first neonatal death (in 1944) occurred about 24 hours after birth, after a labor of 38 hours, 5 minutes. This patient was anesthetized deeply in the delivery room in an attempt to relax a contraction ring in order to carry out a breech extraction. After failure of this attempt, a cesarean section was performed necessitating a second anesthesia. Autopsy findings revealed partial expansion of the lungs and dilatation of the heart.

The second neonatal death (in 1947) occurred in the infant of a mother who was subjected to cesarean section after a labor of 54 hours, 48 minutes. There was moderate difficulty in the extraction of the head at the time of operation. The baby did poorly and died 18 hours after delivery. The principal findings at autopsy were moderate aspiration of amniotic fluid and incomplete expansion of the lungs.

The third fetal death (in 1947), after a labor of 31 hours, 15 minutes, occurred in the infant of a mother who also received a double anesthesia; the first in a fruitless attempt to remove a broken bit of glass catheter from the bladder, the second at the time of the cesarean section. After the first anesthesia there was a good deal of doubt as to the presence of a fetal heartbeat. The baby was stillborn. The principal autopsy findings were a small tear of the tentorium cerebelli and moderate aspiration of amniotic fluid.

Comments

This statistical analysis has been presented in an attempt to record and evaluate as carefully and objectively as possible the results obtained in cases of delivery by cesarean section on the obstetrical service at Bellevue Hospital, where the transperitoneal lower segment procedure is the operation of choice for abdominal delivery. The particular group of patients was chosen for the analysis, not because such prolonged labors are advocated or desirable, but because it represents those cases in which abdominal delivery presents the greatest hazards from infectious complications and hemorrhage, and, second, because it presents an opportunity to study the results of this type of operation

combined with the prophylactic use of the sulfonamides and penicillin, and the judicious use of blood transfusions. The results here presented of necessity justify the efficacy of the management of these cases as outlined.

Summary

1. From June 2, 1940, to Dec. 31, 1949, there were 500 cesarean sections performed on the obstetrical service at Bellevue Hospital; seventy (14 per cent) of these operations were done after labors of 30 hours or more.

2. The seventy patients with prolonged labors in all but one instance were delivered by low flap cesarean section.

3. Fifty-nine cases (all treated by the lower segment transperitoneal type of operation) in which sulfonamides and/or penicillin were used prophylactically intra and/or post partum are analyzed in some detail. All but three had ruptured membranes for an average duration of about 39½ hours.

4. Cephalopelvic disproportion was the most frequent primary indication for operative intervention; the most frequent secondary indication was uterine inertia.

5. The over-all morbidity calculated on the scale described was 54.4 per cent. Local infection of the uterus, herein described as endometritis, was the most frequent cause for morbidity, occurring in 88.9 per cent of all morbid patients.

6. Eight cases in which grossly purulent amniotic fluid was discovered at operation are analyzed in detail.

7. In the latter half of the series, along with a higher incidence of hemorrhages, there was a more marked increase in the administration of blood transfusions; 79.3 per cent of all patients received transfusions at operation or immediately postoperatively.

8. There were three fetal or neonatal deaths, an incidence of 5.5 per cent. In two cases double anesthetics were administered, the first because of a complication of labor, the second for the operation.

9. During the period June 2, 1940, to Dec. 31, 1949, there were no deaths following low flap cesarean section after labors of 30 hours or longer from hemorrhage or infection.

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VAGINAL SMEARS IN THE EVALUATION OF OVARIAN DEVELOPMENT AND ACTIVITY*

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VAGINAL smears need no elaborate introduction. Their physiologic significance in the human being was brought into focus by Papanicolaou in 1933. His subsequent work, with that of many others, is gradually accumulating and disseminating data pertinent to the delineation of follicular activity and hormonal effects. Physiologic and diagnostic implications will give vaginal smears a place among the ever-increasing number of laboratory aids only if their clinical worth is established. Revealing as they do desquamated cells from the stratified squamous epithelium of the vagina, they vary with the degree, rate, and duration of follicular activity. The epithelium of the entire sexual tract is similarly affected.¹ That of the vagina is most easily accessible and, once its activity is fully understood, physiologic responses to stimulation and evaluation of activity from these responses become as promptly available as similar ones in the laboratory animal. To insure the proper interpretation of our findings, we must (a) establish a definition of terms, and (b) thoroughly envision the activity of the ovaries, the effectors. With such prerequisites, analysis will lead to the solution of medical and physiologic problems within the widespread area of ovarian influence.

Material Studied

During the last ten years, every woman seen in my private practice, regardless of age or symptomatology, received examinations which included serial vaginal smears throughout a control period, a period of therapeutics, and periods of follow-up depending upon necessity and cooperation. Excepted were those in whom disease or new growth was discovered. In addition, vaginal smears were examined from (a) volunteers who were apparently normal, (b) others who contemplated pregnancy, and (c) some who were apprehensive about sterility but were not as yet ready to put themselves to the test.

The individual smear is obtained with ease, processed with a single differential stain² and ready for reading in a short time.† Findings are recorded upon a background consisting of a careful history of the patient, type of complaint, and the observed status of development.

In general, it was found that follicular activity of the ovary is a pivotal occurrence which influences hormonal, autonomic, and functional balance. Physiologic efficiency, or a functional normal, depends upon the attunement of a degree of intrinsic development to a chronologic age.

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†DF 77, an experimental stain by Papanicolaou, generously supplied by him, has been used with success by the writer for the last eight years. The secretion is obtained with a pipette, spread evenly on a slide, and fixed immediately in equal parts of alcohol (95 per cent) and ether. Stain is applied for a minute or two. The slide is carried progressively through two washings of alcohol (95 per cent), absolute alcohol, and xylol. It is then mounted under a cover glass with Permount. In general, cornified cells are revealed as red cells, all others are blue.

Functional Levels of Ovarian Activity: Ovarian Age

The ovary undergoes specific changes from birth to maturity.³ The most significant factors pertaining to its functional efficiency are concerned with follicular growth and maturation. There is random growth of follicles up to and beyond puberty. With approaching maturity, a "favorite follicle"⁴ outstrips others in growth and assumes a functional role, and, schematically expressed, random growth of follicles ceases as cyclic activity ensues in coordination with the activity of the anterior lobe of the pituitary.⁵ Thus, the ovary passes through various functional levels of activity, each with its own individual potentialities. If these levels could be assayed within their proper chronological intervals, ovarian age could be determined just as bone age can be read in the roentgenograph. Such an evaluation will reveal (1) an infantile ovarian age, (2) a prepubertal ovarian age, (3) a pubertal ovarian age, and (4) a mature ovarian age. Since maturity does not end its functional existence, ovarian activity, regressing from that point, reverses itself as the ovary passes through premenopausal levels to a menopausal state.

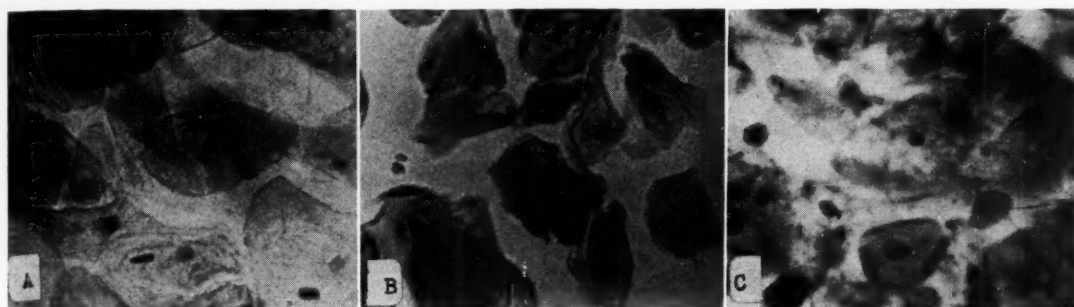


Fig. 1.—Infantile ovarian age.

A. Stratification and cornification in a newborn, 8 hours old.

B. Eight days later. Desquamation to deeper layers. Deterioration of superficial cells.

C. At age 13 years. Absence of secondary sexual characteristics. Note atrophic deep cells and debris in absence of hormonal activity.

1. The Infantile Ovarian Age.—

Follicular activity is at a minimum during infancy and early childhood. Primary follicles begin to grow, but the ova within them do not survive long.^{3, 6} The follicles deteriorate in atresia or small cyst formation before a significant amount of hormones can be elaborated.

At birth, the vaginal epithelium shows considerable stratification and cornification due to maternal hormones.⁷ However, cornification, polygonal shapes, and pyknosis do not reach the degrees attained when more mature epithelia are similarly stimulated (Fig. 1, A). Involution is prompt. Within a few days, the cornified cells disappear, desquamation is carried to deeper layers in the stratification, and cells on the surface, unsupported by hormones, deteriorate before desquamation (Fig. 1, B).

Smears with low levels of stratification which reveal no evidence of activity over long periods of time constitute the criteria of the infantile ovarian age, no matter at what chronologic age they are found (Fig. 1, C).

2. The Prepubertal Ovarian Age.—

With elaboration of estrogen the primary follicles attain higher degrees of growth, which result in the development of differentiating features of the female sex, ultimately producing the secondary sexual characteristics. From this early period of childhood to prepubescence, vaginal smears progress through all changes found in the follicle-ripening phase of the normal sexual

cycle.^{8, 9} These may be recognized in the (a) increasing levels of stratification, (b) gradually increasing degrees of cornification, and (c) more obvious pyknosis and polygonal shapes of the larger cells. These changes are gradual and become obvious only after relatively long intervals. Bleeding episodes are rare because of the nonreactivity of the immature endometria.¹⁰ As puberty is approached, smears may resemble an estrogenic peak (Fig. 2, A, B, and C).

The prepubertal ovarian age is characterized by vaginal smears which reveal moderate levels of stratification and cornification, but with no evidence of cyclic or rhythmic alterations which usually lead to bleeding phenomena.

3. The Pubertal Ovarian Age.—

Follicular activity reaches higher levels until an estrogenic peak initiates an intermittent pituitary-ovarian interrelationship.⁵ A "favorite follicle"⁴ will play a physiologic role. Depending on the growth and inactivation of this follicle, cycles of activity become apparent. The evaluation of puberty depends upon the fate of the follicle.

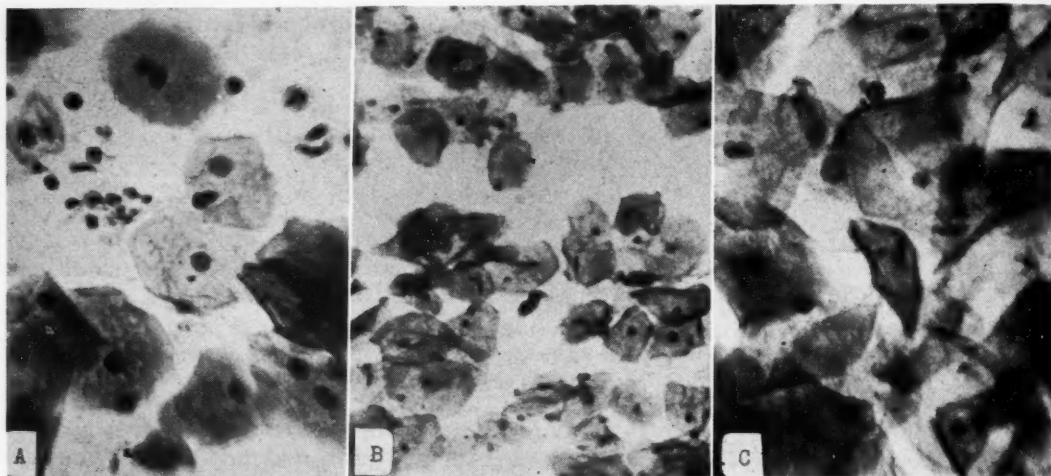


Fig. 2.—Prepubertal ovarian age.

A. At age 22 years. Sexual characteristics well developed by prolonged follicular activity at a relatively low functional level. Menses infrequent, no menstrual molimina. Moderate stratification and slight cornification. No alterations in serial smears. Hormonal stimulation balanced with rate of desquamation producing well-defined cells.

B. At age 18 years. Well developed. Continuous premenstrual tension. Menses irregular by months. Large flat cells, many well cornified. No alterations in serial smears. (Cumulative hormonal effects in this case have produced severe hemorrhagic episodes.)

C. At age 14 years. Delayed menarche. Swollen striated breasts and profuse vaginal discharge. Smear resembles an estrogenic peak. No alterations in serial smears. Note lack of uniformity in size of cells and degree of pyknosis, both signs of immaturity. (Menarche three months later.)

The fate of the follicles in the pubertal ovarian age:

1. Follicle ripening followed by prolonged functional activity (follicle persistence): A high estrogenic peak is attained which persists up to bleeding phenomena. Smears reveal the supporting effects of estrogen which keep the rate of stratification higher than that of desquamation. Precornified cells therefore are not found (Fig. 3, A). Even after bleeding has ceased, the cornified zone is practically intact. Meanwhile, new follicular growth maintains and increases the high estrogenic level (Fig. 3, B).

2. Follicle ripening followed by early collapse and deterioration: Gradually increasing stratification and cornification take place. After a moderate

estrogenic peak, smears reveal a poised state of highly cornified cells which soon begin to show signs of deterioration. Desquamation takes place to lower levels of stratification, depending upon the interval between the collapse of the follicle and ripening of subsequent follicles. Deep cells from the outer basal zone may be found. Intervals between such cycles are not uniform (Fig. 4, A and B).

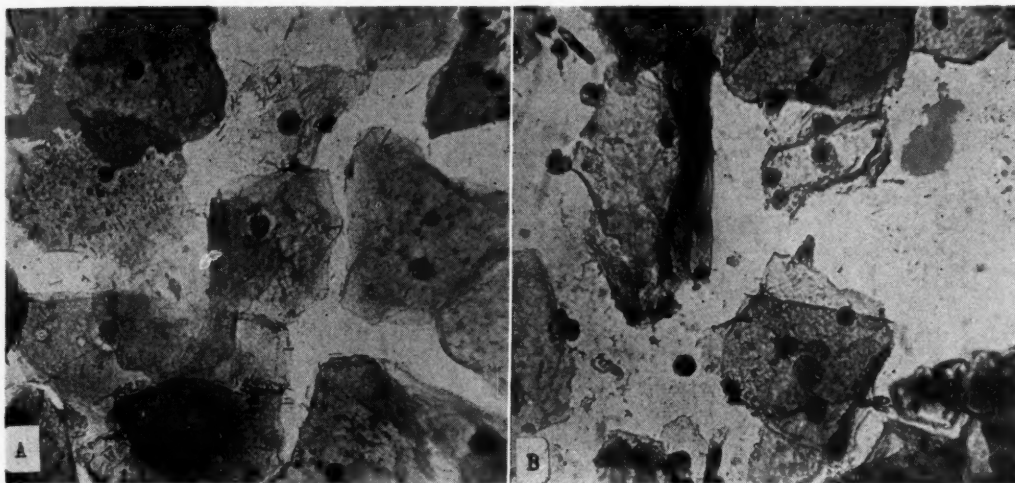


Fig. 3.—The pubertal ovarian age.

A. At age 17½ years. Hypermenorrhea, a profuse flow every 10 to 20 days lasting about a week. Day 9, a highly cornified smear due to overstimulation. Menstrual bleeding 48 hours later.

B. After eight days of bleeding, day 10 of following cycle reveals practically same degree of cornification. Rate of estrogenic elaboration overcomes effects of desquamation.

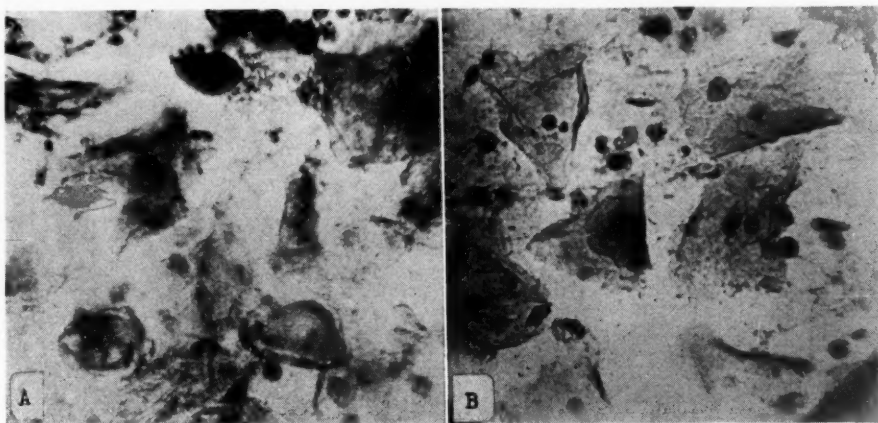


Fig. 4.—Pubertal ovarian age. Age 13½ years. Irregular menses every 6 to 8 weeks. Hemorrhagic bleeding lasting 10 to 20 days.

A. Day 14 after bleeding 11 days. Shows depths of stratification to which desquamation had taken place since collapse of previous follicle. Debris and deterioration indicate that follicle ripening has not started.

B. Day 35. Highly cornified cells with relatively large nuclei indicating rapid follicle ripening. (Subsequent smears showed gradual deterioration and desquamation to relatively low levels before next menstrual flow began.)

3. Follicle inertia: In this group fall the vast majority of cases which hover between the two extremes described above. They are the questionable cycles which intervene between normal cycles in most women but occasionally

constitute a threshold beyond which ovarian potentialities cannot rise. Follicles ripen, but their climax, be it rupture or atresia, is followed by slow inactivation. Hormonal elaboration wanes; regressive phenomena gradually appear; the alterations in the smear vary according to individual gradings.

(a) Instead of a normal luteal phase, precornified cells from the subcornified layers appear. Superficial cells are vulnerable to surrounding irritants; they are not well defined; their cell membranes become permeable to debris; clumping increases as early premenstrual characteristics take the place of what would normally be an early, proliferative luteal phase. So gradual are these changes that fairly well-maintained stratification may be errone-

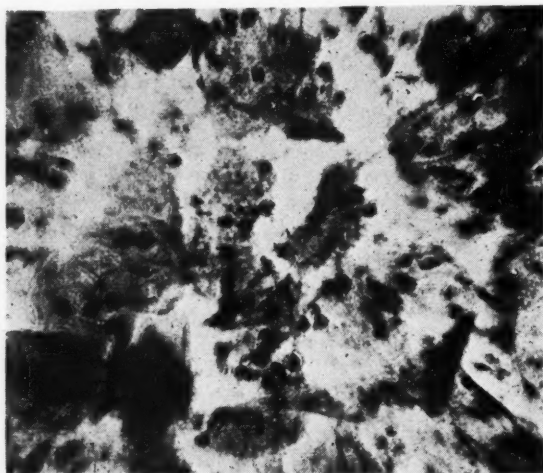


Fig. 5.—Follicle inertia. Five days after an estrogenic peak, day 20. The dark areas are remains of cornified cells. Intracellular debris, deterioration, and cell-membrane defects are characteristics of the premenstrual phase. No signs of non-cornified cells except those from the precornified layers. No change in serial smears to day 30, when menstruation began.

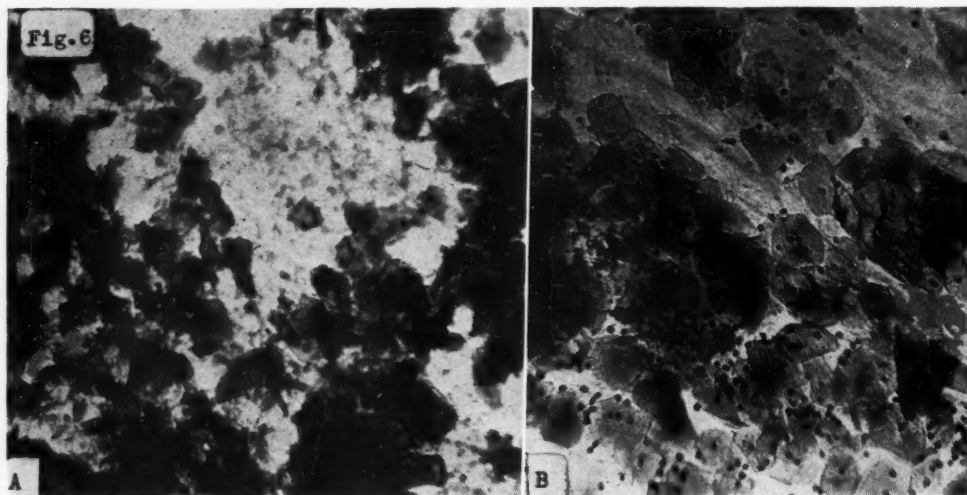


Fig. 6.—Follicle inertia.

A. Day 21, similar to Fig. 5. Clumping and deterioration indicate early hormonal withdrawal.

B. Day 25, same cycle. Clumps are thinner and smaller. Fresh flat cells have appeared, some partially cornified. This new follicle ripening progressed to day 28, when menstruation started. (After four days of bleeding, smear revealed well-advanced follicle ripening characteristic of an approaching estrogenic peak.)

eously interpreted amid debris, sediment, and the relatively small but thick clumps of atropic cell fragments (Fig. 5).

(b) Frequently, after such a picture is discovered, signs of fresh follicle ripening become obvious. The smear clears, faint traces of cornification appear in the cytoplasm of cells which are increasing in size, so that, by the time the menstrual flow is expected, a fully bloomed follicle ripening phase, with or without fibrination, is discovered. Unretarded by the menstrual flow, this follicle may rupture immediately after the normal flow or very early in the next cycle (Fig. 6, A and B).

(c) Occasionally, the estrogenic levels recede so slowly as to delay follicle ripening after the intervening menstrual flow. Smears resembling the premenstrual stages are present for as long as eight or ten days, and only then can relatively normal follicle ripening be recognized. Rupture and ovulation, if they take place at all, are delayed, and may take place during the premenstrual phase (Fig. 7).

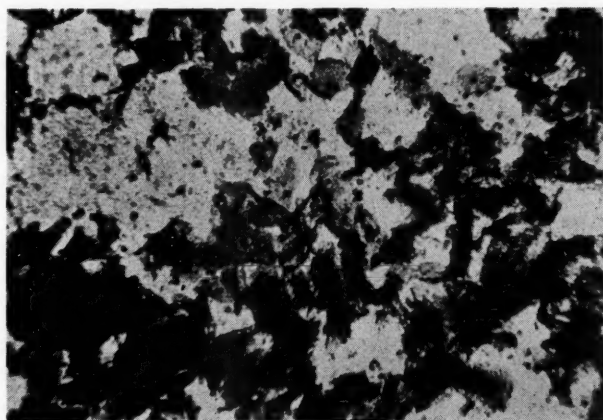


Fig. 7.—Follicle inertia. Day 6. Dark cells and twisted shreds are remains of cornified cells of previous cycle. Noncornified cells are atrophied. No signs of follicle ripening. Smear is identical with those which preceded the previous bleeding episode. (Follicle ripening was first recognized on day 10; the estrogenic peak on day 24; menstrual bleeding started on day 29.)

Follicle inertia, so called because activity, though present, neither reaches a level necessary for a normal cycle, nor regresses sufficiently to allow for normal phase differentiation and timing, produces phenomena which suggest the possibility, as expressed by Papanicolaou, Traut, and Marchetti, that "the absolute dependence of every uterine stage on a corresponding ovarian stage is an axiom which may eventually lead to wrong interpretations and conclusions."^{1a} Such a dissociation of the follicular cycle and the menstrual cycle is more specifically emphasized by the opinion of Evans and Swezy, that ovulation can take place at any time in the menstrual cycle.¹¹

The pubertal ovarian age is characterized by a follicle-ripening phase, an apparent transitional phase, but little or no luteinization.

4. The Mature Ovarian Age.—

The follicle during the mature ovarian age reaches Graafian proportions, ruptures, and liberates an ovum; the ovum is fully prepared to withstand the physical stresses of migration; the remaining follicular structure undergoes luteinization. The vaginal smears depict the varying characteristics of this activity.

1. The follicle-ripening phase: In from nine to nineteen days¹² follicle ripening is climaxed by an estrogenic peak. As a result of a closely packed zone of cornification, pyknosis and polygonal shapes are relatively uniform, egress of leucocytes is inhibited, while the high acidity inhibits bacterial growth. The smear is therefore, uniform, clean, and leucopenic (Fig. 8, A and B).

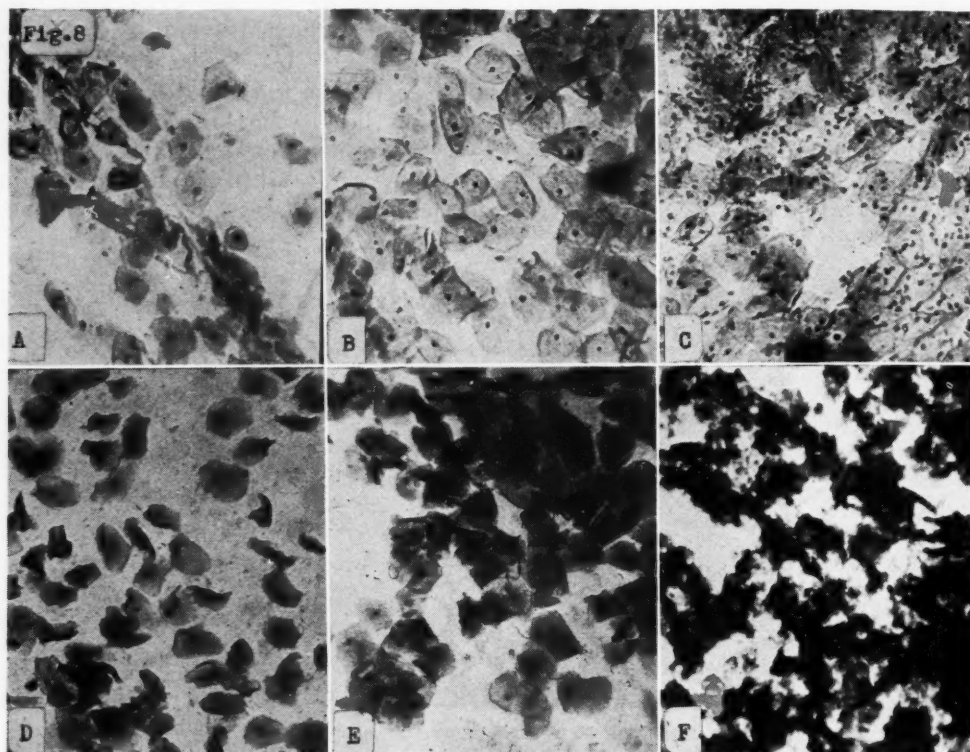


Fig. 8.—The mature ovarian age: a normal sexual cycle.
A. Follicle ripening. Some of the large cells are partially cornified.
B. The estrogenic peak. Only occasional noncornified cells are seen in the typical smear. Note leucopenia.
C. Abrupt appearance of leucocytes (ovulation).
D. The cornified cells twist and curl. The flat round cells are fairly uniform, have vesicular nuclei, and increase in number rapidly as the cornified cells diminish and deteriorate.
E. Rapid increase of the noncornified functionalis cells. They are well defined, uniform, and display remarkable uniformity of vesicular nuclei.
F. The functionalis cells, too, undergo deterioration as the premenstrual phase approaches. Finally, clumping, complete loss of cellular identity, and accumulation of debris end the cycle.

2. The follicle-transition phase: Estrogenic withdrawal causes deterioration and desquamation of the cornified zone. Thus, an abrupt appearance of leucocytes takes place, to be followed in a day or two by the appearance of noncornified cells. The picture of a clean smear of cornified cells upon which a sudden leucocytosis appears indicates ovulation (Fig. 8, C). While the smears are being studied, such an inference must depend upon subsequent changes. Until the effects of undeniable luteinization are discovered, the writer prefers to call it the "estrogenic peak."

3. The phase of luteinization: Cornified cells deteriorate and decrease in number as noncornified functionalis cells appear.^{8, 9} These cells are smaller, round or oval, have relatively large vesicular nuclei, and are evidence of the luteal phase (Fig. 8, D and E). They are rapidly produced, rapidly desqua-

mated, begin to crowd and deteriorate as the corpus luteum wanes. Soon, cytoplasm becomes filled with debris and leucocytes, cell outlines become ragged and premenstrual deterioration reaches a point where cellular elements are no longer discernible. In the meantime, only shreds of former cornification can be detected. Menstrual bleeding follows (Fig. 8, F).

5. *The Premenopausal Ovarian Age.*—

As the potentialities of the ovary wane, primary follicles are reduced in number, the functional levels of the ovary regress gradually to an inactive state during which time the pubertal and prepubertal functional levels may be recognized. However, since irregularities of estrogenic elaboration affect mature end organs (endometrial), bleeding disturbances are more common than in the advancing prepubertal and pubertal ages.

The premenopausal ovarian age is characterized by irregular follicle-ripening phases, prolonged transitional phases, and, very frequently, poor luteal phases. Endometrial hyperplasia, the results of unbalanced and cumulative stimulation, may persist independently of current follicular activity.¹³ Once again, the various fates of the follicle influence physical signs.

Typically, the menopausal ovarian age may produce signs of estrogenic depletion, in which case smears reveal "atrophy," desquamation to the lower levels of stratification without signs of regrowth. In such cases, the resemblance to the infantile type of smear is apparent. Ovarian activity, apparently, is absent.

A preliminary account of vaginal smears in early pregnancy has been previously reported.¹⁴ Corroboration still awaits available cases in sufficient number.

Comment

We are dealing with a reaction motivated by the follicular activity of the ovary. To what extent the individual follicle approaches its functional maturity or how many follicles take part in the production of hormones determines the stimulating force. Timing is involved. It becomes a matter of obtaining quantitative estimates of such stimulation, not in terms of units but in terms of measured fluctuations as discerned from day to day.

Up to the present time, the endometrium has been our main criterion of ovarian activity. The introduction of a change to the vaginal smear must produce a tendency to compare the two in search of correlation, if not preference. The reactivity of both must be compared, therefore, in anticipation of controversy.

Endometrial reactivity in other than normal circumstances is unpredictable; bleeding may occur from any stage of its development; there is no uniform correlation between degrees of hyperplasia and degrees of follicular activity.^{13, 16, 17, 18} Persistent states and the fact that there is little loss of tissue during episodes of bleeding from estrogenic endometria^{16a} indicate that proliferation takes place during progressive follicular growth but that no reversal of such phenomena follows regression of estrogenic levels.

One of the most significant observations made from the many smears examined was that stratification and cornification proceeded and receded in direct proportion to the amount of ovarian hormones involved, whether intrinsically elaborated or therapeutically administered. Desquamation from surface epithelia is always to be expected. This implies loss of layers. Since regrowth, or renewal of lost layers, can occur only with resumed follicular activity, superficial cells found in the smears at all times delineate current follicular activity, which, after all, is the object of our search.

The application of our findings to physiologic and gynecologic problems is a broad subject. A comprehensive enumeration of specific illustrations would require too lengthy a discussion. Such a list must grow as the subject unfolds.

The physiologic aspects concern the absence of an exact or invariable relationship between the ovarian cycle and the menstrual cycle. That it is not always present is the opinion of Papanicolaou,^{1a} Evans and Swezy^{11, 15} and others. This view, which includes the opinion that ovulation may occur at any time during the menstrual cycle, is corroborated by the illustrations of the various degrees of follicle inertia. Follicle ripening does not always begin with the onset of menstrual bleeding.

Infertility, the various menstrual disturbances, the delayed menarche, the amenorrheas, mittelschmerz, ovulation bleeding, pregnancy and its disturbed states are but a few of the diagnostic problems which deserve further investigation. In the absence of evidence of disease, deviations from the normal or from the expected may point to devious interrelationships between ovarian activity and the rest of the body disturbed by an unbalanced (autonomic) system.

Vaginal smears are of great import in the evaluation of gonadotropic hormones, specifically, follicle-stimulating hormones. Vaginal-smear alterations following their use have been reported.^{19, 20} Advancing ovarian age, as might be expected in the developing immature female, is the only evidence available to us that ovarian stimulation may be taking place. An approximation of the ovarian age to the chronologic age is the only evidence of a relatively normal sexual development.

The writer denies originality in any of the data concerning ovarian development and activity or endometrial reactivity. Clinical observations have been reported, interpreted, and found to corroborate established concepts of physiologic activity.

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THE OVARIAN BRENNER TUMOR; ITS GROSS AND MICROSCOPIC PATHOLOGY

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WHILE the ovarian Brenner tumor has been recognized for over 50 years, its rarity has permitted only a few isolated studies devoted to the pathology of the neoplasm although many relevant case reports have appeared in the literature.

The purpose of this investigation is to study the pathology and histogenesis of the neoplasm utilizing 23 specimens available to the author.

The specimens were derived from surgical and autopsy material submitted to the Institute of Pathology of the University Hospitals of Cleveland and from other sources. The study is based on multiple sections of each tumor stained with hematoxylin and eosin, together with numerous special stains as will be indicated. Serial sections were utilized in studying the histogenesis of the neoplasm.

Gross Pathology

The tumors in this series were variable in size. The smallest was of microscopic size, while the largest weighed 370 grams. Many larger tumors are reported in the literature, including a specimen weighing 6.8 kilograms, and when they occur in combination with ovarian cystadenomas even larger masses result.

The solid tumors were round or ovoid, smooth, firm, pale yellowish-gray, and slightly bosselated. Some were pedunculated. On transection the smaller masses were usually well demarcated from the surrounding stroma and were slightly bulging, gray or yellowish-gray. There was a delicate whorling apparent in many of the larger tumors. Cysts occurred in many of the neoplasms. They varied from microscopic size to cavities measuring several centimeters in diameter. The larger cysts contained a translucent pale yellowish-brown pseudocolloid which was usually firm after formalin fixation and in this respect resembled the locular content of many of the serous cystadenomas while that of the pseudomucinous cystadenomas more commonly remains fluid.

In the gross the tumors must be differentiated from the ovarian fibroma and thecoma. While the sudanophilic properties of the thecoma are useful in its recognition, differentiation from the fibroma is more difficult and in many cases is impossible.

Microscopic Pathology

The tumors were composed of irregular columns and masses of polyhedral cells separated by stroma. There was compression of the connective tissue at the periphery of the cell masses in many tumors. Here the reticular fibers were closely applied producing argyrophilic laminations that varied in width and density. Stromal cells in these sites frequently showed fatty degeneration and contained numerous droplets of fat when stained with sudan IV or sudan black.

In some tumors this process was not limited to the periphery of the cell masses but also involved wide areas of the intervening stroma. Such extensive fatty degeneration explains in part the yellow color of many of the gross specimens.

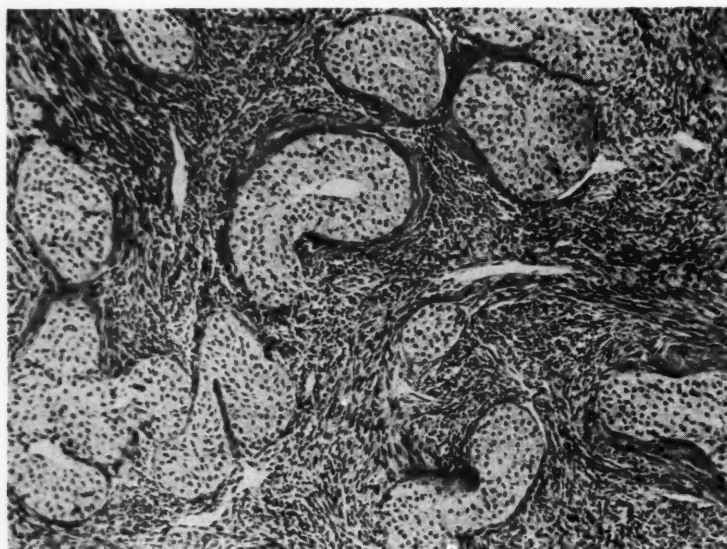


Fig. 1.—Typical solid Brenner tumor with hyalinization of connective tissue about cell masses. (Hematoxylin and eosin stain, $\times 94$.)

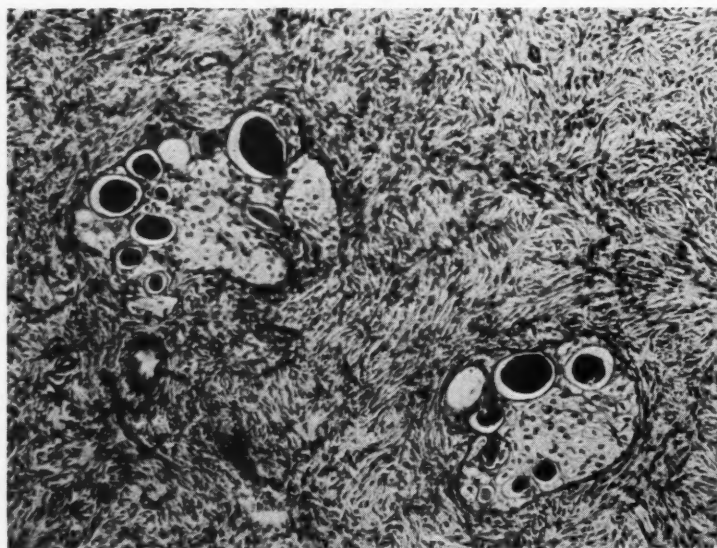


Fig. 2.—Brenner tumor containing microcysts. (Periodic acid Schiff's stain, $\times 117$.)

Surrounding each cell mass there was frequently a well-defined zone of hyalinized connective tissue. In many neoplasms the hyalinization was more widespread and involved larger areas. Calcification was common in the latter sites. In those tumors with widely dispersed cell masses the intervening stroma contained collagenous connective tissue fibers, ovarian stromal cells which resembled smooth muscle cells but lacked myofibrils, and less commonly a few

fragmented elastic fibrils. There were also scattered macrophages containing pale yellowish-brown granular pigment in hematoxylin and eosin preparations. Subsequent study revealed these cells to be identical with the ceroid-containing macrophages occurring about the corpus luteum in regression.¹ In several sites the macrophages occurred in large aggregates at the periphery of the tumor. At no site were they in close proximity to a corpus luteum. Their presence is probably explained on the basis of impaired lymphatic drainage produced by the tumor.

Many of the tumors showed a paucity of vascular spaces yet necrosis was not common. Follicular remnants were not seen within the tumor but were frequent at its periphery. Their position and the apparent compression suggest that the tumor growth is by expansion rather than by invasion and the ovarian elements are displaced to the periphery where they form a pseudocapsule about the neoplasm.

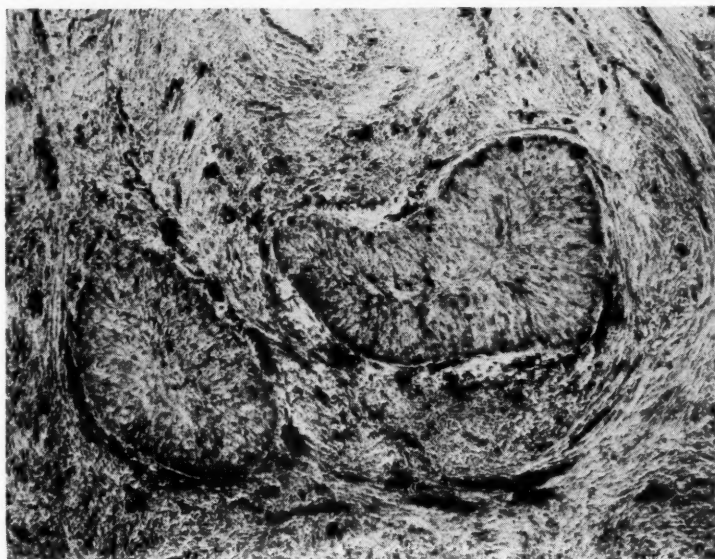


Fig. 3.—Typical solid Brenner tumor with abundant fat located at the periphery of the cell masses and in the intervening connective tissue. (Sudan black, $\times 124$.)

Both columns and isolated cell masses occurred in the tumor. When serial sections were examined many of the supposedly isolated cell masses proved to be transected columns. These extended for variable distances throughout the tumor and ranged from 30 to over 300 microns in diameter. The columns showed extensive arborization in some sites and knoblike expansions were encountered along their course and at their terminal portions. Following an irregular course throughout the tumor at least a few of the columns were connected with superficial cell inclusions that resembled the Walthard cell rests or peritoneal bodies. This will be discussed further when the histogenesis of the tumor is considered.

The polyhedral cells making up the epithelial component of the tumor showed varying degrees of compression. Their cell membranes were well defined when examined with Heidenhain's iron-hematoxylin stain. Intercellular bridges or foci of keratinization were not observed. The cell cytoplasm was finely granular or slightly vacuolated when stained with hematoxylin and eosin. With Heidenhain's iron-hematoxylin vacuolization was more apparent. The latter

is probably due to the glycogen content of the cells since with Best's carmine stain there was a fine red granularity to the cytoplasm of many of the cells. Since only formalin-fixed material was available for study the absolute glycogen content of the cells could not be determined. Isolated cells contained droplets of fat when stained with sudan IV or sudan black and were undoubtedly degenerative.

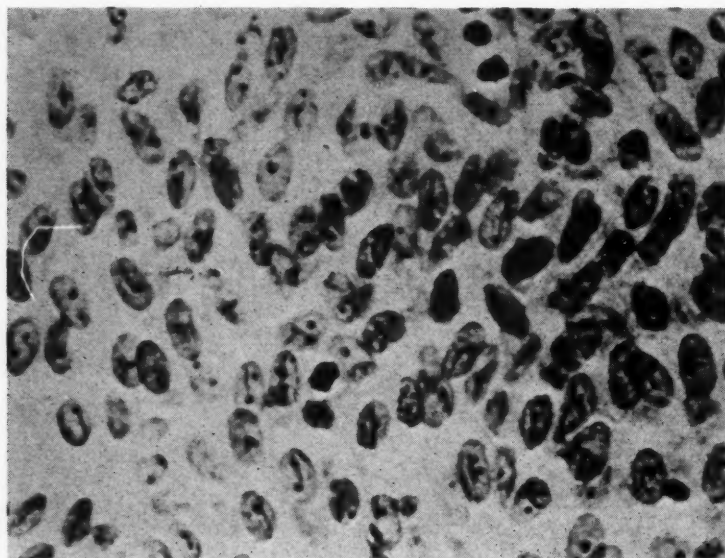


Fig. 4.—Linear chromatin depositions in nuclei of Brenner tumor. This condensation of chromatin may be related to nuclear infolding. (Heidenhain's iron-hematoxylin stain, $\times 920$.)

The cellular aggregates presented several interesting nuclear features. Wrinkling and infolding of the nuclear membranes was prominent in many sites, being clearly apparent in Heidenhain's iron-hematoxylin preparations. It seems unlikely that it is the result of pressure alone since it is not constant in sites where pressure is most marked. The infolding of the nuclear membrane and the so-called "longitudinal grooving" of the nucleus has been studied by several authors, among them Arey,² who was unable to explain its significance satisfactorily. In order to investigate this feature the Feulgen³ reaction was employed to examine the nuclear chromatin. In such preparations there was condensation of nuclear chromatin underlying the nuclear membrane. This resulted in a linear deposition of chromatin adjacent to the site of nuclear infolding in some sites. More commonly, however, the linear deposition of granular chromatin was arranged parallel to the long axis of the nucleus and was not conclusively related to infolding of the nuclear membrane. Thus, the so-called "longitudinal nuclear grooving" represents a linear deposit of chromatin which more commonly occupies the central portion of the nucleus. This feature is not limited to the Brenner tumor but is also observed in the Walthard cell rest and less commonly in the lining epithelium of the pseudomucinous cystadenoma. Cells of many other tissues show this characteristic which is prominent in the Sertoli cells of the testes. The remaining nuclear chromatin was finely granular with one or two larger aggregates observed throughout the nucleus. Mitoses were not observed.

Microscopic cysts were present in most of the tumors examined by multiple sections. These were frequently small and were solitary or multiple in the cell masses. The earliest change toward cyst formation consisted of an increased

granularity of the cytoplasm of contiguous cells. These cells underwent hypertrophy and tended toward a radial arrangement about a small central space. When stained with mucicarmine at this stage the cells contained small, widely dispersed, poorly defined secretory granules. The more mature cysts were lined with flat, cuboidal, or columnar epithelium. The latter cells possessed well-defined cell membranes and terminal bars. When stained with Heidenhain's iron-hematoxylin a striate border was sometimes observed over the free border of the cells. Such epithelium contained well-defined secretory granules when stained with mucicarmine although the granules were less numerous than those observed in active mucus-secreting epithelium. True goblet cells were infrequent. When stained with Best's carmine stain many of the columnar cells contained glycogen in variable amounts.

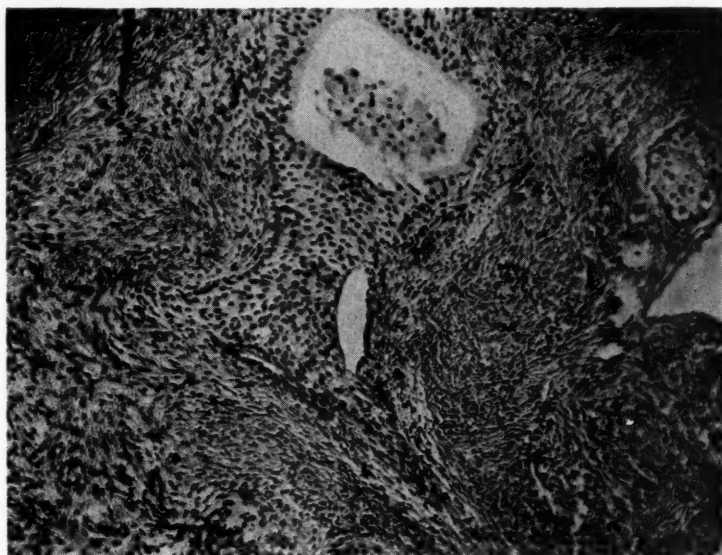


Fig. 5.—Cell mass in Brenner tumor containing cyst lined by columnar epithelium. (Hematoxylin and eosin stain, $\times 190$.)

Larger cysts were formed by coalescence of smaller spaces. These were lined by simple flat, cuboidal, or columnar cells and in some sites by stratified epithelium. Most of the cysts were of only moderate size since the compression of the lining epithelium by the cell secretion limited the development of the cystic spaces. While those cysts situated within hyalinized connective tissue were for the most part of limited size, those situated in loose stroma tended to be somewhat larger and were more commonly lined by tall columnar cells exhibiting less evidence of compression.

The cystic spaces contained amorphous acidophilic material and large deeply acidophilic globules together with desquamated cells and small fat droplets. The cyst content stained with mucicarmine, Best's carmine, and with the periodic acid Schiff's reagent.⁴

Histogenesis

Two specimens were selected for additional study by means of serial sections. The first specimen containing a small subcortical tumor was examined in its entirety. The sections revealed numerous apparently isolated cell aggregates lying immediately beneath the ovarian surface. As many as three such masses were seen in a single high-power field. Many of these were in contact with the

overlying germinal epithelium and were made up of small polyhedral cells. Morphologically they were comparable to the Walthard cell rests or peritoneal bodies although they were more numerous than is usually encountered. A study of the mesovarium, mesosalpinx, and uterine tubes from the same case revealed only a rare peritoneal body. Further study of the ovary revealed many of the supposedly isolated cell masses to be expanded portions of short cell cords which

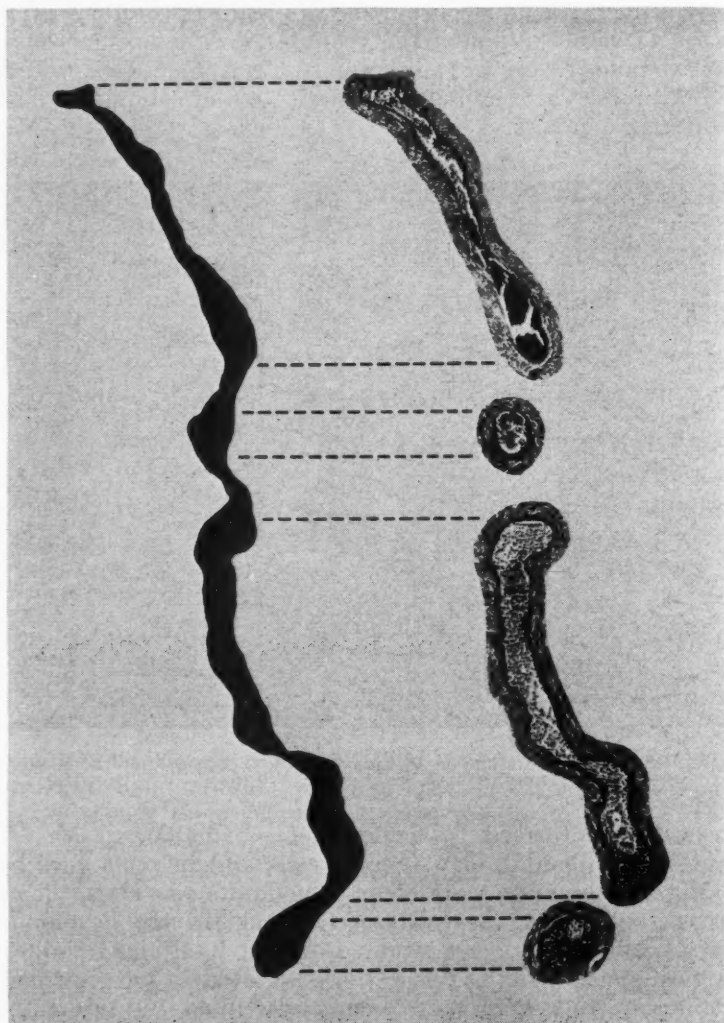


Fig. 6.—Silhouette of reconstructed cell cord, unusual in that it is more direct than is commonly seen. The more superior aspect corresponds to the ovarian surface, while the inferior limits lie within the Brenner tumor proper. Photomicrographs of representative segments of the cell cord are shown. (Hematoxylin and eosin, $\times 64$ [reduced one-third].)

extended for varying distances throughout the ovary. When the ovary was reconstructed it was apparent that many long cell cords were also present and several of these were traced without interruption between superficial inclusions and the tumor proper lying deeper in the ovary. In addition there were numerous small cell masses and short cords arranged in linear distribution between the cortex and the tumor. These masses were separated by hyalinized connective tissue bands of varying width.

The second specimen studied by serial sections included only a segment of a larger tumor. The superficial cell inclusions identified in the first specimen were also encountered here, but were fewer in number and more widely separated. The compressed ovarian tissue at the periphery of the tumor showed more extensive hyalinization than was apparent in the original specimen and was more limited in extent. On reconstruction there were short cell cords and isolated cell masses located along definite pathways extending from the surface to the tumor but these were fewer in number than those observed previously. In all, eleven separate cell cords were traced for varying distances into the ovary. While all of these arose in superficial inclusions none could be traced without interruption into the tumor proper. Those most nearly demonstrating continuity revealed breaks that measured approximately 20 microns in length. Most of these columns extended through dense hyalinized connective tissue.

In summary, the findings on serial section indicated many superficial cellular inclusions morphologically identical with the Walthard cell rests. These were apparent in both specimens studied but were more numerous in the ovary containing the small subcortical tumor. The inclusions proved to be expanded terminal portions of longer cell columns which in one specimen extended into the tumor. In both specimens there were short segments arranged along definite pathways extending from the surface in the direction of the deeper tumor. These were broken by connective tissue bands of varying width and density.

Comment

The ovarian Brenner tumor is a benign neoplasm made up of solid or cystic masses and columns of polyhedral cells surrounded by ovarian stroma which is commonly compressed and hyalinized. The tumor is uncommon. Among approximately 42,000 surgical specimens submitted to the Institute of Pathology, there were only 12 cases recorded, although a review of the ovarian tumors might have disclosed additional specimens.

The tumors were usually unilateral. Only 3 of the 23 cases in this series were bilateral although a detailed study of both ovaries was possible in only 7 cases. Since in many instances only a single ovary is available for examination, the statistical incidence of bilateral involvement is unreliable. Although a comparatively large percentage of the earlier reported cases were bilateral, Dockerty and MacCarty,⁵ in a series of 10 cases, and Novak and Jones,⁶ in a study of 14 cases, found no instance of bilateral involvement. Fox,⁷ in a comprehensive review of the literature including 170 cases, accepted only 10 bilateral tumors to which he added 3 additional cases.

While usually recognized in the postmenopausal years, the tumors in this series were recognized most commonly during the fourth and fifth decades; the youngest age represented being 27 years and the oldest 77 years.

Most of the tumors recorded in the literature occur in the white race. In this study only 2 of the 18 cases in which race is recorded existed in Negroes.

Earlier workers believed the tumor to have an endocrine function. In only 9 cases was the uterus available for examination. Of these, 7 contained fibromyomas and 5 contained polyps of the endometrium or cervical canal. Atrophy of the endometrium was seen in 3 specimens. Cystic hyperplasia of the endometrium was present in one specimen together with a small focus of well-differentiated adenocarcinoma. The associated endometrial hyperplasia observed by other investigators was present in one case, although only a limited number of uteri were available for examination. The uterine lesions encountered might well explain the various menstrual irregularities which have been attributed to the presence of the tumor.

Coexisting ovarian tumors were present in three cases. A struma ovarii was present in one patient with bilateral Brenner tumors while in another case with unilateral involvement there was a serous cystadenoma in proximity to the tumor. One specimen with a small Brenner tumor contained a pseudomucinous cystadenoma. Examination of the mesosalpinx, mesovarium, and uterine tubes was possible in 14 cases. While rare isolated peritoneal bodies were identified they were no more frequent than usually encountered and remained small and discrete.

The histogenesis of the tumor has received the attention of many authors. Brenner,⁸ after whom the tumor is named, believed it to be of granulosa-cell origin. Similarly the rete ovarii has been implicated. Meyer,⁹ among others, suggested an origin from the small cellular inclusions located in the subserosa of the uterine tube, mesosalpinx, and mesovarium. These masses were first described by Werth,¹⁰ who demonstrated their origin from peritoneum. Subsequent investigators, among them Green, Peckham, and Gardner,¹¹ reached similar conclusions as did Walthard¹² in studying ovarian inclusions. These solid or cystic aggregates are encountered in the infantile ovary and are made up of polyhedral cells whose nuclei show prominent linear chromatin depositions. All the epithelial variations encountered in the adult Brenner tumor may exist in the masses which are thus miniature counterparts of the adult tumor. While many of the inclusions are the result of embryonic rests, there is some evidence to suggest that they may also be the result of prosoplastic metaplasia of peritoneum in the adult. It remained for Plaut¹³ to demonstrate origin of the Brenner tumor from such inclusions. The small subcortical tumor in this series was an excellent specimen for examination. Serial sections showed intact cell cords extending from superficial inclusions into the underlying tumor. In addition there were small cords and isolated masses arranged along definite pathways between the cortex and the tumor suggesting previous intact epithelial tracts. Thus this tumor offered conclusive proof of continuity between tumor and Walthard inclusions. The second and larger specimen could be examined only in part and did not show conclusive evidence of this mode of origin. There were, however, short cell cords arranged along definite linear pathways between the cortex and the tumor. Origin from deeper inclusions might also explain those tumors limited to the medulla of the ovary since small isolated aggregates also exist in this site as well, although in the author's experience they are much less frequent.

The association of the Brenner tumor with other ovarian neoplasms is of interest. Meyer⁹ and Novak and Jones⁶ agree in the belief that the pseudomucinous cystadenoma may occasionally arise from the Brenner tumor. Step sections of the single example of coexistence in this series revealed no evidence of continuity, but this alone does not disprove such an origin. Similarly it has been suggested that some ovarian fibromas may have their origin in the Brenner tumor. For this purpose the author reviewed 50 ovarian fibromas in an attempt to demonstrate rare cellular inclusions. While in many instances only a single microscopic section was available for examination, no such aggregates were found.

Summary

The Brenner tumor is an uncommon benign ovarian neoplasm which is usually unilateral in location. The solid or cystic tumors are variable in size, usually firm, pale yellowish-gray, and well circumscribed. A study of their histopathology reveals polyhedral cells arranged in masses and columns frequently surrounded by degenerate and hyalinized connective tissue. When

cysts occur, they are lined by flattened, cuboidal, or columnar epithelium containing glycogen and secretory granules staining with mucicarmine. In this study of 23 cases, serial sections of a small subcortical tumor revealed definite continuity between superficial inclusions and the tumor. A second tumor studied did not reveal conclusive evidence of such an origin.

The author wishes to express his appreciation to Miss Ethel Lieb for expert technical assistance in this study.

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ASYMMETRY OF THE UTERUS IN EARLY PREGNANCY

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IN 1836 Jacquemin¹ pointed out that bluish discoloration of the vagina and vulva was associated with early pregnancy, and in 1880 Hegar² described the softening of the lower uterine segment as a means of diagnosis. The pelvic findings of ectopic pregnancy were publicized by Campbell's extensive monograph in 1842,³ and furthered by the works of Parry⁴ and Tait,⁵ but it was not until 1890 that the examination of the pelvic contents as an intrinsic part of the antenatal physical examination was utilized even in the larger teaching clinics of Europe.

The knowledge of the changes in size and shape of the uterus in early pregnancy is necessarily recent, and it has been only since 1900 that attention has been generally drawn toward asymmetry of the uterus.

In 1893 two French authors, Tedenat⁶ and Pyesch,⁷ both of Montpellier, independently published descriptions of patients who had signs and symptoms which were indistinguishable from those of ectopic pregnancy, but who delivered spontaneously by vagina at term. A similar case, terminated by operative interference, in which the fetus was found in a "diverticulum" of the uterus, was described at the Obstetrical Society of Bellevue, in New York, in 1897.⁸ The condition described in these early reports was characterized by lower abdominal pain, bleeding, and a pelvic mass, associated with early pregnancy, but which was definitely proved (by delivery) not to be an ectopic pregnancy. Within the next decade other cases were reported, and a definite term of "angular pregnancy" was applied in 1903.⁹

The diagnosis and terminology soon fell into disrepute because of the difficulty of differentiating with accuracy the so-called angular pregnancy from tubal or interstitial pregnancies. Authorities of the time, Couvelaire,¹⁰ Pinard,¹¹ and Bar,¹² debated inconclusively the actual existence of the condition. After a number of years the term was lost almost completely in this country, and may still be found only occasionally in the French and Spanish literature.

The present communication is concerned with reinvestigation of this condition in the light of present knowledge, avoiding if possible the controversial issues which caused it to be discredited. Therefore, it must be stated that we are not describing a specific anatomical condition, but only a sign and symptom complex characterized by asymmetry of the uterus, pain, and uterine bleeding associated with early pregnancy. In this way we may avoid the classical argument as to whether the anatomic lesion is an interstitial pregnancy or an implantation of the zygote in the cornual aspect of the uterine cavity.

Frequency

The frequency with which gross asymmetry of the uterus of early pregnancy occurs is not known. De Lee¹³ stated that early in pregnancy all uteri soften irregularly. How often this irregular softening becomes a definitely describable asymmetry is not recorded, but we are inclined to agree with Bar¹² that it is frequent.

Unfortunately, data cannot be given on the frequency with which asymmetry of the uterus, abdominal pain, and bleeding occur, for the lack of recognition that the so-called "angular pregnancy" has enjoyed makes collection of such data impossible. In the past decade there have been approximately 25,000 obstetrical admissions to Gallinger Municipal Hospital, and during this time there have been 10 recognized and proved instances of symptomatic asymmetry of the uterus. It is by no means believed that this is an accurate and all-encompassing figure, for, even though the condition is recognized as an entity by the staff of this hospital, undoubtedly many cases of mild nature pass through as threatened abortions or with other incorrect diagnoses.

During the last ten years at this hospital, one patient with an asymmetric uterus and abdominal pain and bleeding had a perforation of the uterus at five months' gestation. We feel that this is a fairly accurate estimate of the frequency of perforation, for this complication should be difficult to misinterpret.

Etiology

The etiology of asymmetry of growth of the normal uterus in early pregnancy is limited to two conditions: implantation of the placenta in a cornual portion of the cavity with irregular softening of that area, and implantation in some portion of the interstitial area of the tube.

Why the fertilized egg should select the ovary, tube, interstitial area of the uterus, or the cornual portion, has been attractively explained by abnormalities of function of the tube; by ectopic decidua in the ovary, tube, or peritoneum; by anatomic distortion of the path to the uterus by adhesions, myomas, or other anatomic defects; and by other less plausible explanations. Needless to state, proof is lacking for any existing theory.

In the patient without anatomic defects of the pelvic organs, it is difficult to believe that the incidence of implantation site is governed to any large extent by other factors than the laws of chance; i.e., that the choice of implantation site would be in proportion to the surface area exposed; therefore, that choice of implantation areas would be fundal endometrium, cornual area of the fundal endometrium, ampullar portion of the Fallopian tube, isthmus of the Fallopian tube, interstitial portion of the uterus, and ovary, in the order named.

Pathogenesis

Asymmetry of the uterus of mild degree will be caused by implantation of the fetus in any area of the uterus not in the immediate vicinity of the midline, either anterior or posterior. The farther from the midline that placentation occurs, the more noticeable will be the asymmetry.

All degrees of cornual and interstitial implantation might be supposed, and the outcome of these varying degrees would depend on at least the following known variables. The likelihood of producing symptoms would be in direct proportion to the distance of implantation from the midline of the uterus (Fig. 1). The degree of infiltration of the wall by the placental trophoblastic layer, which could possibly depend on the blood supply to that particular area, would be an important factor. Also of importance would seem to be the ability of the uterine muscle in that area to hypertrophy, to multiply,

and to stretch, so as to accommodate the growing product of conception in constricting quarters.

From Figs. 2 and 3, we may see that varying degrees of cornual implantations, angular pregnancies, and interstitial implantations are merely a question of anatomic differentiation. As the conceptus grows, these anatomic boundaries are changed so rapidly that they are dependent wholly on the ability of that portion of the uterine or tubal wall to accommodate. Asymmetry of the uterus following delivery is frequently seen, and is explicable by irregular growth. Diverticulum formation of the uterine wall by the placenta is described in the literature,¹⁴ and we have two proved instances. Diverticulum formation with rupture of the sac has been repeatedly described under the name of "interstitial pregnancy," and "angular pregnancy." That the tube itself has accommodated a term fetus seems undoubted.¹⁵ This latter merely demonstrates variability in ability to accommodate, even by such a thin-walled structure as the Fallopian tube.

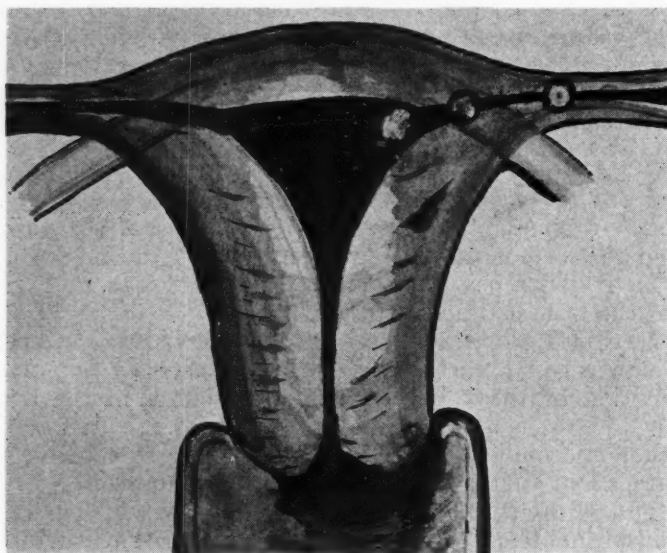


Fig. 1.—A schematic drawing which illustrates the degrees of angular or interstitial implantation of the fertilized ovum.

Symptoms

The time of onset of the symptoms of this condition is extremely variable, but they rarely appear before the eighth week or after the twenty-second week of gestation. In general, symptoms which begin at about the eighth week have disappeared by the twelfth week. In four instances in which the condition has been seen by us, the symptoms began at the eighth week, in one instance at the twelfth week, and in one at the sixteenth week of gestation. Lizona,¹⁶ who reported 7 instances in which spontaneous rupture occurred, noted the rupture of 3 at ten weeks, 1 at sixteen weeks, and 1 at twenty-two weeks.

As has been noted, by far the greatest number of patients who have asymmetrically enlarging uteri are asymptomatic save for the evidences of early pregnancy. In the patients who develop other symptoms, the most common one is pain. It was noted in all of our cases, and is described in practically all those quoted in the literature. This pain, like that in ectopic pregnancy, is extremely variable, but usually begins in the lower abdomen, and is localized more or less on the affected side. It is described as constant, dull, intermittent, and sometimes excruciating. Radiation is not characteristic.

The next most frequent symptom is that of uterine bleeding. It occurred in most of our patients, and in from 60 to 75 per cent of those reported in the literature. The type of bleeding varies from moderate staining to severe hemorrhage.

The passage of tissue is amply described. This material may be decidua; however, the incidence of spontaneous abortion is from 20 to 30 per cent.

Signs

The abdominal signs in the early stages of pregnancy both in the asymptomatic and symptomatic groups show no characteristic deviations from normal. If rigidity, rebound tenderness, or shifting dullness develop, only the diagnosis of perforation must be considered, and the point of implantation becomes merely of scholastic value.

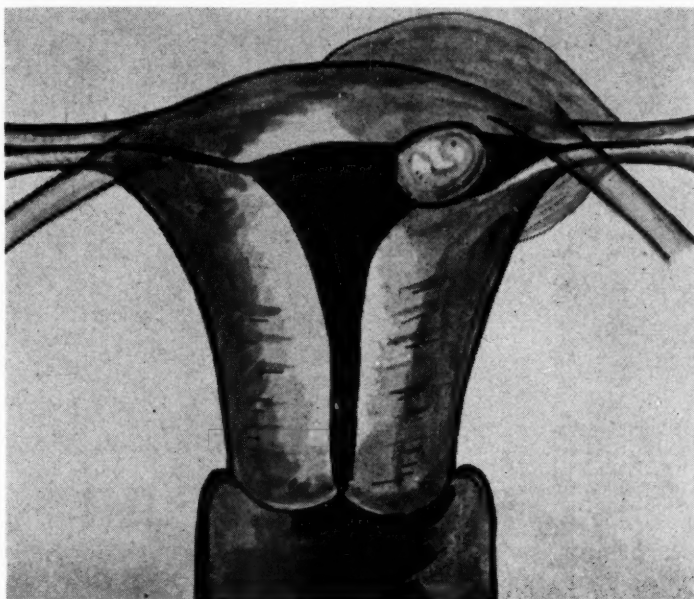


Fig. 2.—Asymmetric growth of the uterus produced by cornual implantation with diverticulum formation. Uterine accommodation and asymmetric growth should allow this type of implantation to eventuate in an intrauterine pregnancy. The round ligament is lateral to the diverticulum.

When the uterus becomes palpable in the abdomen, asymmetry may be made out only early, for very soon the organ is completely and symmetrically filled by the product of conception. However, in a few instances the uterus will maintain some semblance of asymmetry all during the pregnancy.

Following delivery, any severe degree of early asymmetry will be detected by the characteristic shape of the uterus, with a greatly hypertrophied horn on one lateral aspect.

Pelvic signs are quite characteristic. The cervix is characteristically softened, and Chadwick's sign is present. Uterine proportions are usually less than would be expected from the period of amenorrhea, and the corpus is thought to be firmer than the consistency noted for this length of gestation. Softening of the lower uterine segment is consequently less noticeable than in normal implantations. What seems to be an associated softened mass is noted in one adnexal region, which characteristically displaces the main portion of the corpus to the opposite direction. Careful examination will frequently

TABLE I. THE SIGNS AND SYMPTOMS COMMON TO ASYMMETRY OF THE UTERUS IN EARLY PREGNANCY AND TO THE MORE FREQUENT ENTITIES WHICH MUST BE CONSIDERED IN THE DIFFERENTIAL DIAGNOSIS

	PAIN	BLEEDING	ADNEXAL MASS	TISSUE PASSED	ACUTE CONDI- TION IN ABDOMEN	SHOCK	ANEMIA	ELEVATED WHITE BLOOD COUNT
Ectopic pregnancy	+	Frequent	+	Frequent	Frequent	Frequent	Frequent	Frequent
Angular pregnancy	+	Frequent	Seemingly none	Frequent	None	None	None	Rare
Threatened abortion	+	+		Frequent	None	None	Occasional	Frequent
Abnormality of fusion of Müllerian ducts	Occasional	Occasional	+	Occasional	None	None	None	None
Appendicitis	+	Occasional	None	None	+	None	None	+
Retroflexed uterus	Occasional	Occasional	None	None	None	None	None	None
Lateral flexion	Rare	Occasional	+	None	Occasional	None	None	None
Salpingitis	+	Occasional	+	None	Occasional	None	None	Frequent
Ovarian cyst	Occasional	Occasional	+	None	Rare	None	None	Rare
Myomas	Occasional	Occasional	+	None	Rare	None	None	Occasional

show that this mass merges into the corpus with no sharp division, and that normal adnexa can be made out lateral to the "mass."

Differential Diagnosis

The common conditions which must be differentiated from asymmetry of the uterus, in order of importance (not frequency), are ectopic pregnancy, appendicitis, spontaneous abortion, and retroflexion of the uterus, as stressed by De Lee. Other complications which may be confused with it are ovarian cysts, solitary myomas, acute salpingitis, and lateral flexion of the uterus.

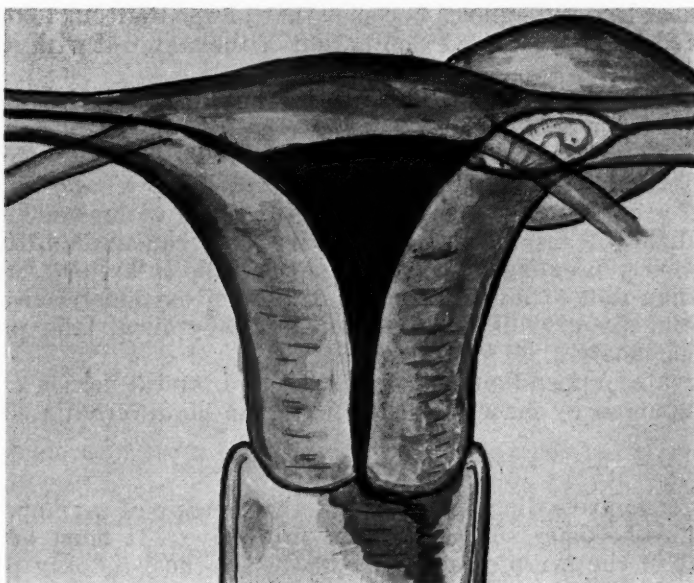


Fig. 3.—Asymmetry of the uterus produced by implantation farther out in the uterine portion of the tube. Growth of this type may be accommodated but would be more likely to produce rupture of the uterine wall. The round ligament is medial to the diverticulum in this instance.

Table I shows the common factors involved in both symptoms and signs in asymmetry of the pregnant uterus, and those associated with the more frequent conditions from which it must be differentiated. It is to be noted that pain and bleeding, which are the most ominous and frequent symptoms and signs, cannot be used to rule out any of the conditions. The presence or absence of an adnexal mass is of great importance, and the characteristics of this mass and its anatomical connections are even more important. It is necessary to identify without equivocation whether or not a mass actually exists, whether it merges into the small firm corpus, and whether the ovary and round ligament can be made out lateral to the mass. Examination under anesthetic should always be carried out in those patients who do not permit careful and exact examination while awake because of obesity or lack of cooperation.

If careful and exact examination can be carried out, it will be found in these cases of asymmetry that the "diverticulum" or "pseudocornu" gradually merges with the uterus. A "pseudo-Hegar's sign," excessive softening of the junction between the mass and the corpus, may render the diagnosis confusing, but in general a definite fusion of the two masses may be determined.

The position of the mass in regard to the corpus will frequently help to differentiate the condition from a tubal pregnancy. It is usually higher and

more anteriorly placed in the pelvis than the ectopic tubal pregnancy, which is usually found in the cul-de-sac and posterior. When the round ligament can be made out, it should be palpated going into the top of the mass, not inserting medial to the mass as occurs in the tubal pregnancy.

Pain on motion of the cervix and on pressure on the mass will be much less noticeable than in the ectopic pregnancy or even in acute salpingitis, and limitation of the mass or other organs of the pelvis will not be as noticeable as in these two conditions.

Study of Table I will also show that the passage of tissue will not rule out threatened abortion or ectopic pregnancy. Occasionally a decidual cast is passed from the nonpregnant horn of a bicornuate uterus. When tissue is passed, the most likely diagnosis becomes that of spontaneous abortion, which may be clarified by microscopic examination of the material with identification of villous processes.

Ectopic pregnancy must be ruled out by laparotomy in the presence of an acute condition in the abdomen or shock.

Elevation of the temperature and white blood count are frequently of value in differentiating salpingitis, ectopic pregnancy, and abortion, but rarely should be changed from the normal in patients with asymmetrical uteri.

Abnormalities of fusion of the Müllerian duct can undoubtedly be diagnosed during early pregnancy in some cases only by inference, but therapy is no different than that of intrauterine pregnancy or asymmetrical uteri; therefore, differential diagnosis is not necessary and may await later pregnancy or delivery for clarification.

Uncomplicated appendicitis, retroflexion, and lateral flexion of the uterus are not accompanied by mass formation, and can be differentiated by careful examination.

Treatment

Once a presumptive diagnosis is made, the therapy of asymmetric uteri in early pregnancy becomes supportive and protective. It must be recognized primarily that in the symptomatic patient the diagnosis is only presumptive, and that the patient is considered to have an ectopic pregnancy until an intrauterine pregnancy can be definitely demonstrated. With this knowledge, it is necessary to observe the patient closely in a hospital where blood and facilities for removing the ruptured viscus are available on immediate notice. With the asymptomatic patient, more latitude may be allowed, but these patients also should be observed at frequent intervals even after the uterus becomes symmetrical, since in rare instances perforation of the uterine wall may still occur.

It is obviously unnecessary and economically unsound to place all patients with asymmetrical uteri in early pregnancy in a hospital for six months, but it is necessary to inform them of the potential dangers, so that early signs of a catastrophe may not be overlooked, and it is necessary to see these patients at frequent intervals.

While in most cases the performance of laparotomy under the mistaken diagnosis of an ectopic pregnancy rarely does irreparable damage, a curettage of the uterus does, and both should be avoided if a presumptive diagnosis of symptomatic asymmetric uterus can be made. It must be stressed that there may be economic conditions and hospital facilities such that procrastination on a patient suspected of an ectopic pregnancy is not justified and may even be dangerous. In such cases, when a reasonable doubt exists that the pregnancy may be intrauterine, it would seem logical to investigate immediately by posterior colpotomy, or by the culdoscope when one is available.

When placentation in the cornu of the uterus has been strongly suspected or known to exist, immediate manual removal of the placenta from the third

stage uterus would seem to be indicated. The excessive use of the Credé maneuver for placental expression or awaiting spontaneous delivery of the placenta may cause the constricting mouth of the diverticulum to become firmly established.

Comment

Undoubtedly several types of abnormal implantation and possibly functional peculiarities may produce the clinical picture of an asymmetric uterus in early pregnancy. The prognosis is somewhat changed according to the actual basic problem, but implantation in a rudimentary horn in a bicornuate uterus, in a proximal portion of the interstitial area of the tubes, or in the angular portion of the uterus may undoubtedly result in abortion, placental incarceration, intra-abdominal rupture, and in the other less serious portions of the picture.

It is necessary to recognize this syndrome not only to be alert to the serious complications which may arise, but to safeguard from laparotomy, hysterectomy, or curettage those patients who have a mistaken diagnosis of ectopic pregnancy, incomplete abortion, or placental incarceration.

It must be borne in mind, of course, that the diagnosis of "angular pregnancy" fell into disrepute because enthusiastic individuals were using it as a blanket diagnosis, covering ectopic pregnancy, adnexal masses, and other obscure pelvic conditions. It is stressed that the diagnosis cannot be made except by exclusion and the passage of time, and that the only excuse for its consideration as an entity is to protect the patient from unnecessary neglect and fetal loss.

Conclusions

A syndrome consisting of asymmetry of the uterus in early pregnancy is reintroduced.

The complications of abortion, uterine rupture, and incarceration of the placenta are possible and not infrequent.

The differential diagnosis and suggested therapy are outlined.

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CYTODYNAMIC PROPERTIES OF HUMAN ENDOMETRIUM*

II. Cultivation and Behavior of Stromal Cells of Human Decidua In Vitro

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ALTHOUGH histologic studies of fixed and stained decidua have been recorded by many investigators, this tissue has rarely been studied in a living functional state. Some applications of tissue-culture techniques to morphologic and physiologic studies of the human female reproductive organs have been reported, but the work is still in its embryonic state. Guggisburg and Neuweiler,¹ Friedheim,² Sengupta,³ Madruzzo,⁴ Sannicandro,⁵ Jones, Gey, and Gey⁶ have studied the human placenta in vitro. The most extensive work has been done by Heim,⁷⁻¹⁴ who cultured human chorion, amnion, decidua, endometrium, and normal and neoplastic ovarian tissue, and summarized the application of tissue culture in the field of clinical gynecology.

In studying decidual cells, Heim⁸ used young human placentas, approximately 6 to 8 weeks old, secured at therapeutic hysterotomies. He claimed optimal results in 2-month-old placentas. After twenty-four hours' cultivation, he described outgrowth of flat cells, epithelial in appearance, with round vesicular nuclei and an abundance of cytoplasm, but made no mention of fibroblastic elements. In placentas over 4 months of age, Heim reported no outgrowth of cells. He did not mention how long he kept his culture growing.

Since the histology of decidual stroma suggests that the cells are of connective-tissue origin and since cells in tissue culture dedifferentiate, it would be logical to expect decidual stromal cells to revert to their original type in vitro. If these two concepts are correct, Heim's observations were incomplete. The present study was undertaken in the hope of demonstrating the expected reversion of decidual stromal cells to mesenchymal elements and thus to corroborate the belief that decidual cells are indeed connective tissue in origin.

Materials and Methods

The specimen used for these experiments was obtained at cesarean section on a 22-year-old primigravida who entered the hospital at twenty-eight weeks' gestation with pre-eclampsia superimposed upon nephrosclerosis. When her condition failed to improve after four weeks of hospital management, it was decided to interrupt the pregnancy. The specimen obtained for culture was received from the operating room under sterile conditions and explanted within two hours after removal. The specimen was divided into two equal portions. One half of the decidual fragment was cut into pieces about 1 mm. square and transferred, until ready for culture, to a watch glass containing Tyrode's solu-

*Supported in part by a grant from the Iowa Division, American Cancer Society.

tion to which 200 units of penicillin and 2 mg. of streptomycin per cubic centimeter had been added. The other half of the specimen was fixed in Bouin's fluid, stained with hematoxylin and eosin, and serially sectioned for histologic study. Microscopically, the tissue used for cultures was composed of decidual stromal cells with a minimum of round cells (Fig. 1).

The cultures were made in large hanging-drop slides as follows: 0.06 ml. (1 minim) of Tyrode's solution was dropped on a square mica cover slip (40 by 40 mm.) and a round cover slip (21 mm.) was placed over it. A drop of rooster plasma was placed on the round cover slip, a small fragment of tissue added, and the drop coagulated by the addition of an equal amount of 20 per cent chick-embryo extract and human umbilical-cord serum. After the plasma had coagulated, the cover slip was inverted over a hollow slide, the chamber sealed with vaseline and paraffin, and the slide placed in the incubator at 37° C. Two hundred sixteen fragments of tissue were explanted.

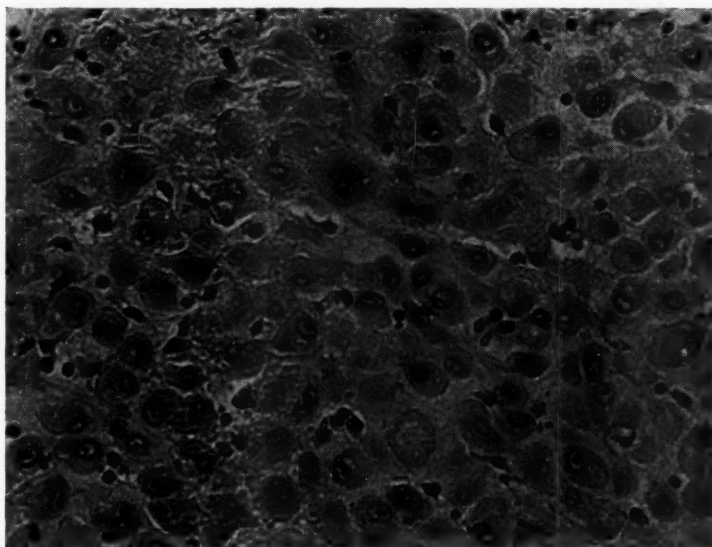


Fig. 1.—Section of decidual stroma used for tissue culture. Bouin's fixative, hematoxylin-eosin stain.

Observations

The cultures were observed at 24-hour intervals and were washed (Tyrode's solution) and refed (equal parts of umbilical-cord serum and 20 per cent chick-embryo extract) every three days.

The latent period for most of the cultures was three days. The first indication of activity in the majority of the cultures was the appearance of fibroblasts in the form of fine, threadlike projections at the periphery of the explants. At five days, the outgrowth of cells was extensive and consisted primarily of loose-to-compact, radially arranged cells, some of which exhibited multipolarity; numerous mitotic figures were seen. The cells were adherent to one another except at the periphery where single cells were in evidence (Fig. 2).

The individual cells ranged from spindle to thin flat cells which were more or less spread out on the cover glass. They contained varying numbers of fat globules and mitochondria. The cytoplasm was thin, delicate, and apparently structureless. The oval nucleus had a thin, scarcely visible membrane, a clear nucleoplasm, and two or more small nucleoli.

On the other hand, some cultures showed sheets of polygonal cells migrating from the tissue explants. These cells contained little cytoplasm and relatively large, round, vesicular nuclei. They resembled to a certain extent the typical outgrowths seen in tissue cultures of epithelium and in no instance showed any resemblance to fibroblastic elements. The only change observed in two weeks of cultivation was an increase in the amount and granularity of the cytoplasm (Figs. 3 and 4).

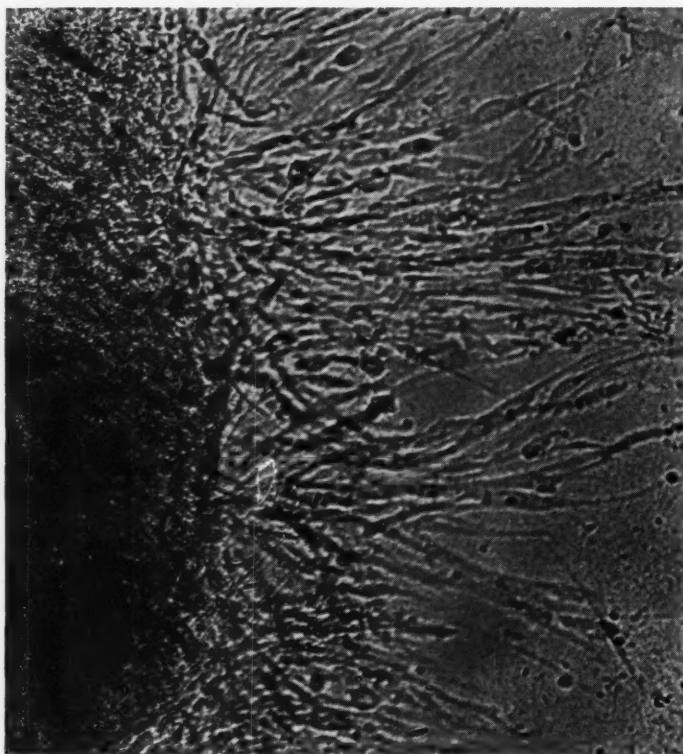


Fig. 2.—Fibroblastic outgrowth from decidual stroma after five days' cultivation. Cultures photographed in the living state. Medium: rooster plasma, 20 per cent chick-embryo extract, and human umbilical-cord serum.

These latter results substantiate Heim's observations that epithelioid cells migrated from explants of decidual stroma. However, in the other cultures fibrocytes were the only elements seen. The difference was evidently not due to the character of the tissue explanted but rather to the medium used. The ill-defined nature of the nutrient (cord serum, embryo extract) immediately suggests that the differences in cell type may reflect variations in the nutrient medium. Since estrogens and progesterone are both present in umbilical cord serum, it is quite conceivable that alterations in their respective concentrations might govern the type of cell outgrowth. Since different samples of serum were used at different times in the experiment, one must speculate about variations in hormonal and other metabolic stimuli, as well as on the effect of quantitative differences in estrogen and progesterone content.

The appearance of two pure types of cells from the same decidual stroma grown in culture can best be explained on the basis of hormonal action. To determine whether such variations were due to hormonal stimulation, it was necessary to find a hormone-free tissue nutrient of precise composition which would support decidual growth.

Although Lewis and Lewis,¹⁵ Drew,¹⁶ Baker and Carrel,¹⁷ Vogelaar and Erlichman,¹⁸ Simms and Stillman,¹⁹ and others had replaced serum or embryo extract with partly or wholly synthetic equivalents, it was not until the work of White²⁰ and Fischer²¹ that satisfactory nutrients of known composition became available. These media, composed of amino acids, vitamins, and inorganic

Fig. 3.

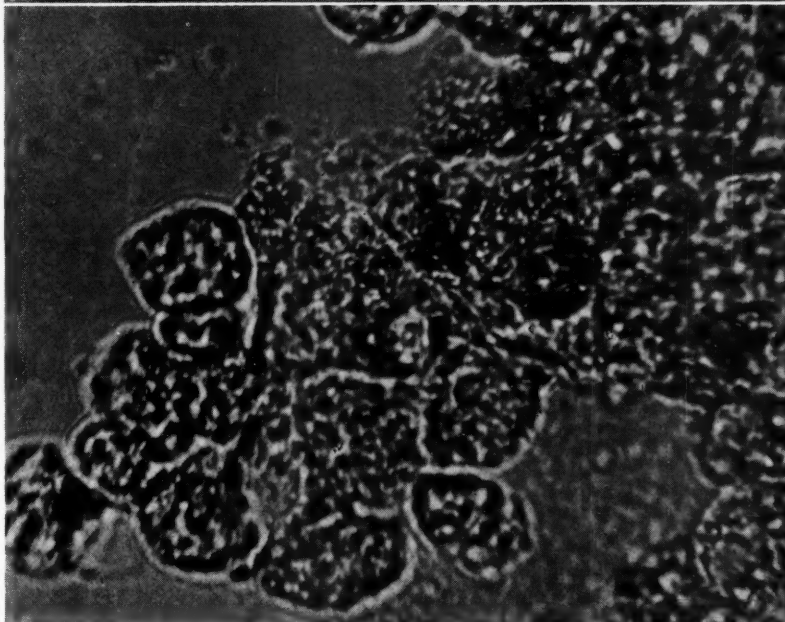
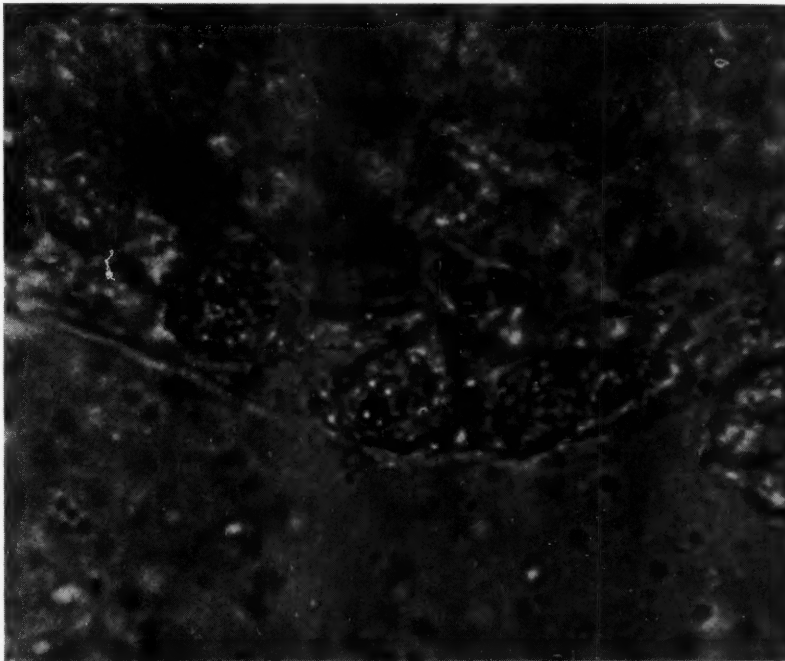


Fig. 4.

Figs. 3 and 4.—Epithelioid outgrowth from decidual stroma after five days' cultivation. Cultures photographed in the living state. Medium: rooster plasma, 20 per cent chick-embryo extract, and human umbilical-cord serum.

ion, supported growth of animal tissues without the addition of serum, plasma, fibrin, or tissue extract.

Methods

The same material was used for this phase of the experiment. The tissue was divided into two parts which were treated as previously described. The portion to be cultured was transferred to a 50-ml. thick-walled centrifuge tube, approximately 20 ml. of Tyrode's solution added, and the tube rotated until the tissue was uniformly distributed. The tube was allowed to stand for a few minutes until the larger fragments to be used for explants settled, leaving a supernate containing cellular debris and blood cells. The supernate was then removed by suction and the fragments washed again. After three washings the fragments were ready for explantation into "square roller tubes."

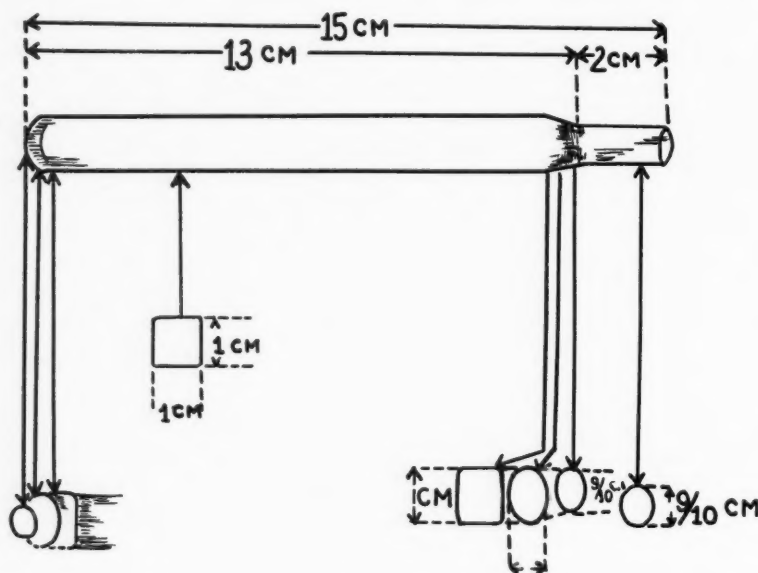


Fig. 5.—Square roller tube for the massive cultivation of tissue in a synthetic medium.

The tube is essentially a square test tube 15 cm. by 1 cm. by 1 cm. (Fig. 5). The flat sides permit good microscopic visualization and its somewhat constricted neck prevents overflow. Uniform distribution of the nutrient is provided while the tube is rotated in the incubator in a roller-tube apparatus.*

The tubes are made from standard Corex glass tubing such as is used for absorption cells.† This glass is uniform, highly polished, and may be cleaned and sterilized in any manner. Two sides of the tube are frosted so that they may be used as cuvettes for spectrophotometric studies. By this technique many biochemical reactions can be carried out in the same vessel in which the tissue is growing.

Tissues cultivated in such tubes lend themselves to detailed microscopic observation and cells may be studied in the living state with "long working distance" phase-contrast optics, even at high magnifications.

The fragments of tissue were distributed evenly over the entire lower surface of the tube by a pipette having a curved tip. Before being placed in the

*The authors wish to acknowledge the work of Gey (Am. J. Cancer, 17: 752, 1933) first to describe a hexagonal tube for microscopic observations of cells cultivated in vitro.

†These tubes may be obtained from Phoenix Precision Instrument Co., 3803 North Fifth St., Philadelphia 40, Pa.

incubation, the tubes were set aside for about two hours at room temperature to "set," so that the tissue fragments would dry onto the glass. If this procedure is not followed most of the tissue will wash loose after the medium is introduced into the tubes. After fixation, the nutrient was added, the tube stoppered and placed in a roller-tube apparatus described by Gey.²²

The fluid nutrient consisted of either White's²⁰ or Fischer's²¹ synthetic medium. Approximately 1 ml. was added to each roller tube; the fluid was replaced every three days. Renewal of the medium was important because of the rapid utilization of the nutrient constituents and the accumulation of toxic metabolic products. Control of H-ion concentration of the cultures was also important since rapidly growing tissue depressed the pH from 7.6 to 6.6 in approximately three days.

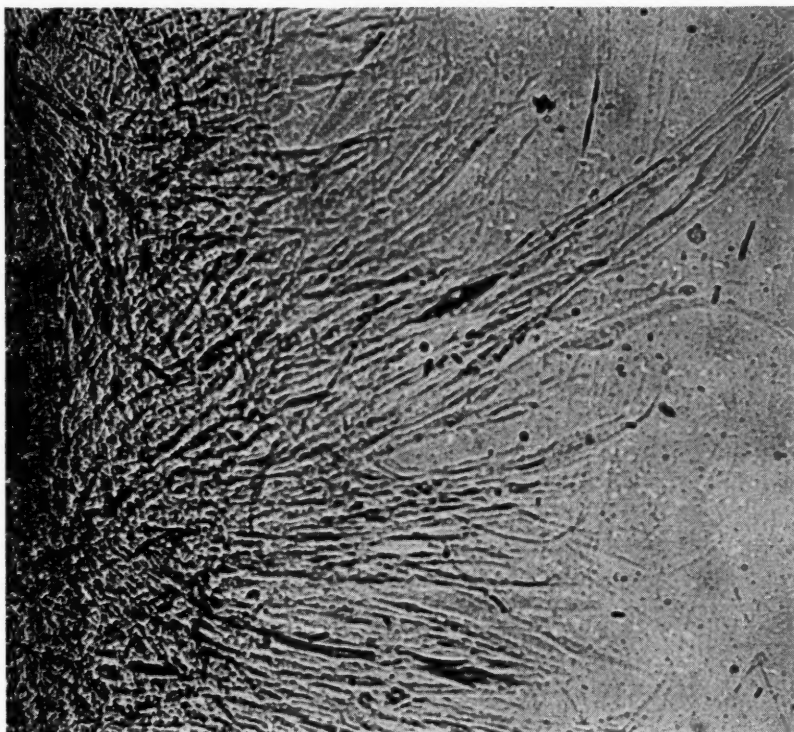


Fig. 6.—Fibroblastic outgrowth from decidual stroma after five days' cultivation in a medium of known composition. Cultures photographed in the living state.

Observations

In both media the first outgrowth of cells from the explants was observed on the third day. Morphologically the cells were identified as fibroblasts. In the beginning the bands of migrating fibroblasts were compact, the cells being close together except at the margins. Subsequently the cells elongated in the direction of migration and the cellular band gradually widened (Fig. 6).

After seven to ten days' cultivation, the 1-mm. explants were surrounded by collars of outgrowth 3 to 4 mm. wide, and the fibroblasts became more definitely spindle shaped. No increase in the granularity of the cytoplasm was observed at this time. The nuclei were large, oval, and optically empty. Fatty degeneration became evident after about two weeks. The intracytoplasmic fat granules disappeared at first upon renewal of the nutrient, but under prolonged

cultivation became more pronounced and permanent. This progressive degeneration continued and the fibroblasts rarely survived as definite areas for more than four weeks. However, in many instances, isolated cell islands continued to migrate away from the original explant for a longer period. In no instance were epithelioid elements found.

Comment

The fact that synthetic media promoted growth of decidual stroma with the same efficacy as natural media offers a means for a controlled experiment. It will now be possible to make accurate analyses of the nutritive requirements for the maintenance and growth of specific cells. It will also be possible to add various hormones to the medium and to note their effects upon the cells. Investigations dealing with the effect of the medium upon the cells and of the cells upon the medium offer many opportunities for studying the dynamic properties of this tissue. Research along these lines may lead to a better understanding of the importance of hormones, vitamins, and co-factors of various kinds in the intermediary metabolism of the cells. It may also be possible to acquire information regarding biochemical events taking place in the cells during growth and differentiation as well as during disease.

While the use of a synthetic medium makes the above concepts tenable, it still does not explain the appearance of two cell types in the embryo extract-serum as compared to one cell type in the synthetic medium. A study is now in progress to determine whether estrogen and/or progesterone played a role in producing this difference.

Summary

Stromal cells of human decidua have been cultivated in vitro in natural as well as synthetic media. In a medium composed of human umbilical-cord serum, rooster plasma, and chick-embryo extract, two types of cells migrated from the explanted decidua. These were fibroblasts and epithelioid cells. In White's synthetic medium, composed of amino acids, vitamins, and the necessary inorganic ions, only one type of cell was cultivated, namely, the fibroblast. The possible role of estrogen and progesterone in the development of stromal decidual cells is discussed.

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AMNION NODOSUM: A LESION OF THE PLACENTA APPARENTLY ASSOCIATED WITH DEFICIENT SECRETION OF FETAL URINE

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MAJOR congenital malformations of the urinary tract, resulting in deficiency of excretion of fetal urine into the amniotic sac, are known to be responsible for some cases of oligohydramnios,^{1, 2} but in the majority of cases reported the placenta is either not described or stated to be normal. However, a small group of placentas has been described, the majority from cases of oligohydramnios, which showed a lesion previously called "amniotic nodules" (*Amnionknötchen*).^{3-8, 10, 11} These placentas show many small nodules, which are most numerous in the placental portion of the amnion; therefore, the name "amnion nodosum" is suggested for this condition.

Although this lesion of the amnion had been observed on two previous occasions in the Department of Pathology at the Boston Lying-in Hospital, it had been considered an incidental finding of unknown significance until a case observed recently served to focus interest on it and to prompt this study.

Materials

The index files were reviewed with respect to lesions of the amnion, and in all suggestive cases specimens were examined microscopically. In addition, the protocols for all infants examined at autopsy from 1931 to the present were reviewed, and all cases with congenital malformations (a total of 200 infants) were selected. The term congenital malformations was used to include abnormalities of development such as Meckel's diverticulum, malrotation of the intestine, and polydactylia, which were never causes of death in this series, as well as the more serious anomalies, congenital heart disease, imperforate anus, tracheoesophageal fistula, diaphragmatic hernia, absent or polycystic kidneys, anencephaly, myelomeningocele, harelip and cleft palate, and others. The placentas of 112 of these 200 infants had been examined both grossly and microscopically, but the microscopic sections did not include the amnion in 37 cases, so that 75 placentas of infants with congenital malformations confirmed at autopsy were available for study. In addition, the placentas of 200 infants who did not die from congenital anomalies were studied as a control series.

Results

Amnion nodosum was found in 8 placentas, 3 from the group of cases indexed under abnormalities of the amnion and 5 from the group of infants who died with congenital malformations. No cases were found in the control placentas. The nature of the fetus associated with each of these 8 placentas is listed in Table I.

In only 2 of these 8 cases were the amniotic nodules noted grossly, but in both they appeared as multiple, firm, rounded, raised yellow spots 1 to 3 mm. in diameter on the amnion of both the membranes and the fetal surface of the placenta.

TABLE I. NATURE OF THE FETUS IN 8 CASES OF AMNION NODOSUM

	CASES
Renal agenesis syndrome ⁹	2
Polycystic kidneys	1
Hypoplastic polycystic kidneys	1
One kidney polycystic and one hypoplastic, anencephaly, imperforate anus and vagina, diaphragmatic hernia, cleft palate	1
Stillborn with multiple anomalies (no autopsy)	2
Stillborn (no autopsy)	1

Microscopically (Figs. 1 and 2) these nodules are seen to be rounded-to-oval masses, most commonly situated on the surface of the amnion, but occasionally embedded in the amniotic mesoderm, or even projecting through it into the cleft between the amnion and chorion. They consist of varying proportions of squamous cells of the amniotic fluid and a matrix of collagen, as shown by Mallory's aniline blue and phosphotungstic acid hematoxylin stains. The amniotic epithelium either is absent in the region of the nodules or partially persists beneath them as small strips or inclusion cysts. The appearance of these structures suggests that they are the result of adhesion of masses of amniotic squamæ to the surface of the amnion, with subsequent degeneration of the amniotic epithelium and invasion of the squamous-cell mass by connective tissue. Masses of amniotic squamæ applied to the surface of the amnion have been observed in some of these sections. These lesions show no relation to squamous metaplasia or to polypoid hyperplasia of the amnion, two processes which seem to be related and which may tend to occur together, nor do they seem to result from degenerative changes in either of these lesions.

Comment

Of the eleven previously described placentas which may be instances of this process,^{3-8, 10, 11} three are rather doubtful,^{4, 6, 8} but the other eight appear to show the same lesion. Of these no mention is made of the condition of the fetus in five cases,^{3, 4, 5, 10, 11} one fetus³ is described as having no major congenital malformations, and two fetuses^{3, 7} had major anomalies of the urinary tract. Thus, it seems that the condition, amnion nodosum, is the result of oligohydramnios rather than the cause, and that it is not associated with oligohydramnios of any given cause. Major congenital malformations of the urinary tract are probably the most common cause of a significant degree of oligohydramnios, and apparently were the factors leading to the production of amnion nodosum in five of the eight cases reported here. However, if amnion nodosum is simply the result of processes set under way by failure of fetal urine secretion, it may occur in some cases of intrauterine death of normally formed fetuses, if abortion is delayed for a sufficiently long period after the death of the fetus. Whether this is the explanation of the occurrence of amnion nodosum in the three placentas of stillborn infants on whom post-mortem examination was not performed, which are described earlier, cannot be stated, but two of these infants had multiple anomalies visible on external examination, so that the presence of major anomalies of the urinary tract cannot be ruled out entirely.

Two possible mechanisms by which oligohydramnios leads to amnion nodosum can be suggested. One is that amniotic squamæ from the abnormally

Fig. 1.

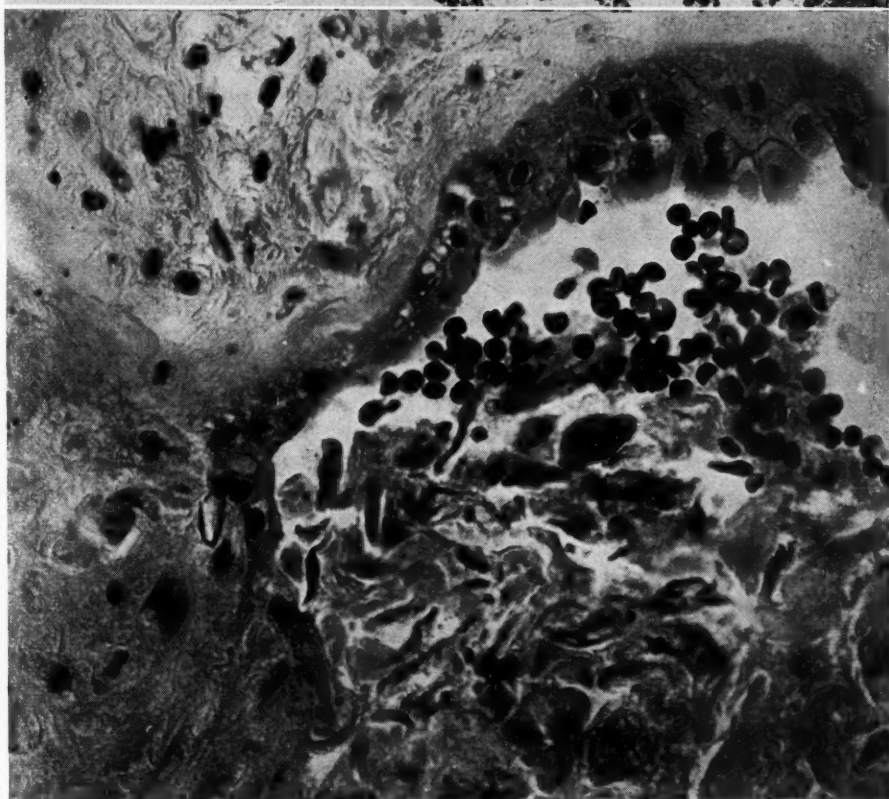
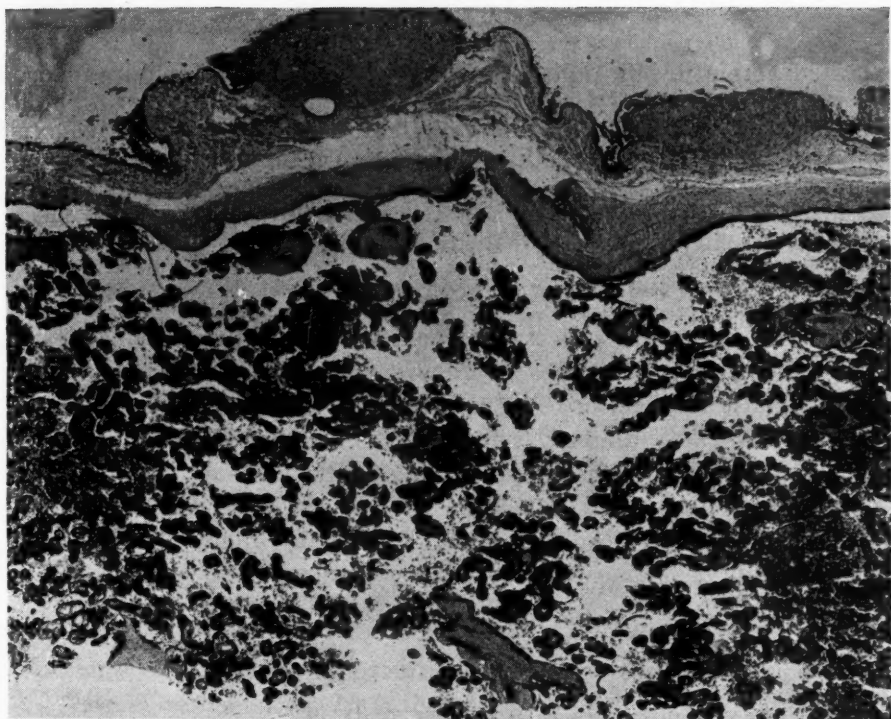


Fig. 2.

Fig. 1.—Amnion nodosum. There is absence of amniotic epithelium in involved areas and projection into amniotic mesoderm (eosin-methylene blue stain, $\times 40$).

Fig. 2.—Border of amniotic nodule showing mass of amniotic squamae partially invaded by connective tissue (eosin-methylene blue stain, $\times 725$).

concentrated amniotic fluid adhere to the surface of the amnion and produce secondary degeneration of the amniotic epithelium; the masses of adherent squamæ are then invaded by the amniotic mesoderm. An alternative explanation is that fetal movements produce traumatic erosion of the amniotic epithelium, and the squamæ adhere to the exposed mesoderm and become incorporated in it as it proliferates. It is not possible to decide between these two possible mechanisms on the basis of the data available.

Summary

Amnion nodosum is a process characterized by multiple, focal lesions of the amnion, consisting of masses of adherent amniotic squamæ partially invaded by amniotic mesoderm. The nodules thus formed have previously been called *Amnionknötchen* (amniotic nodules). This report is based on a study of amnion nodosum occurring in the placentas of eight stillborn infants or infants with major congenital renal anomalies. The study suggests that amnion nodosum is the result of processes set under way by oligohydramnios, caused most commonly by deficiency of fetal urine excretion.

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PLASMA ACETYLCHOLINESTERASE ACTIVITY*

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VARIOUS investigators have reported that pregnancy and the toxemias of pregnancy are accompanied by changes in the activity of various enzymes in the blood.¹ Zeller and associates² and others^{3, 4, 5} have reported that plasma (or serum) acetylcholinesterase (ChE) was depressed significantly during normal pregnancy. Herschburg and co-workers⁶ observed a more pronounced depression of serum cholinesterase in women with toxemia of pregnancy. The present report deals with the plasma ChE in three groups: (1) healthy adult women who were not menstruating or pregnant, (2) normally pregnant women, and (3) women with toxemia of pregnancy. In addition, this study includes tests for plasma activators or inhibitors, as well as the effect of daily doses of Sodium Amytal on the plasma ChE activity.

Methods

All patients in this study were from the obstetric and gynecologic services of the Chicago Lying-in Hospital. Their ages were between 25 and 30 years. The control group of patients were healthy women who were not menstruating or pregnant. No particular day during the menstrual cycle was selected for drawing blood, since it has been shown² that variation among individuals in plasma ChE is greater than the variation encountered in an individual menstrual cycle. Normal pregnant women from the fourth to the fortieth week of gestation were selected for this work. More than 75 per cent of the normal pregnant women studied were in the last trimester of pregnancy. The patients with toxemia of pregnancy were in the last trimester. These were carefully selected as representative cases of pre-eclampsia-eclampsia. They exhibited edema, proteinuria, and hypertension. In three patients the diagnosis of pre-eclampsia was changed later to hypertensive toxemia of pregnancy. Two patients of the toxemic group had eclampsia. Both of these patients were studied within two hours after a convulsive seizure.

The plasma was prepared by letting 3.0 ml. of blood into standard heparinized tubes. Heparinized blood was then centrifuged. Any plasmas which contained hemolyzed red blood cells were discarded. All assays were made within two hours after bleeding. Duplicate assays were done, using 0.1 ml. and 0.2 ml. of heparinized plasma. Acetylcholinesterase (ChE) was measured manometrically according to the method employed by DuBois and Mangun,⁷ which employs a test system containing 0.3 ml. of 0.1M acetylcholine chloride in a final volume of 3.0 ml. of calcium-free Ringer's bicarbonate buffer (0.025M NaHCO₃, 0.15M NaCl, and 0.04M MgCl₂). After tipping the acetylcholine into the major compartment of the vessel, the system was gassed with 95 per cent nitrogen and 5 per cent carbon dioxide for five minutes in a 38° C. water bath.

*This work was supported in part by the Dr. Wallace C. and Clara A. Abbott Memorial Fund and the Chicago Lying-in Fiftieth Anniversary Research Fund on Eclampsia and Puerperal Fever.

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Readings were taken for the following thirty minutes at five-minute intervals. All ChE determinations are expressed in cubic millimeters (c.mm.) of carbon dioxide produced per ten minutes per 0.1 ml. of heparinized plasma. The method described by Beveridge and Lucas⁸ was used to investigate the presence of activators or inhibitors in the plasma of 15 of the patients studied.

Results

Table I summarizes the plasma ChE activity in normal nonmenstruating nonpregnant women (controls), in women during normal pregnancy, and in patients with toxemia of pregnancy. In 19 control women the average ChE activity was 51.6 c.mm. CO₂/ten minutes/0.1 ml. of heparinized plasma with a standard deviation of ± 7.66 . In 59 normal pregnant women the average value was 41.5 c.mm. CO₂/ten minutes/0.1 ml. heparinized plasma with a standard deviation of ± 7.60 . This is 80.0% of the mean obtained for the control women. Using the Student t test⁹ the means of these two groups are significantly different. The p value is less than 0.01.* The difference in determinations in several women at the beginning and at the end of gestation was only 2 per cent. The plasma ChE determinations showed no systematic change referable to the day of gestation. In 19 women with toxemia of pregnancy the average ChE value was 33.4 c.mm. CO₂/ten minutes/0.1 ml. of heparinized plasma with a standard deviation of ± 8.80 . This value is 80.0 per cent of the mean for normal pregnant women; using the Student t test the p value is less than 0.01.† The plasma ChE activity of women with toxemia of pregnancy was 64.7 per cent of the mean for control women. The difference in the means was highly significant. No correlation was noted between the ChE values and the severity of the toxemia. Two eclamptic patients had values of 29.6 and 33.9. Deletion of three cases in which the diagnosis was subsequently changed to hypertensive toxemia did not significantly alter the mean (34.2 c.mm. CO₂/ten minutes/0.1 ml. of plasma).

TABLE I. PLASMA ChE ACTIVITY IN NORMAL YOUNG ADULT WOMEN (CONTROLS), NORMAL PREGNANCY, AND TOXEMIA OF PREGNANCY

GROUP	NUMBER OF PATIENTS	MEAN*	S. D.†	PER CENT OF CONTROL
Control	19	51.6	7.66	
Normal pregnancy	59	41.5	7.60	80.0
Toxemia of pregnancy	19	33.4	8.80	64.7

*Figures express ChE activity in c.mm. CO₂/ten minutes/0.1 ml. of heparinized plasma.

†Standard deviation.

The protocol of a typical experiment to test for the presence of activators or inhibitors in the plasma in the three groups of women is given in Table II. Five experiments, each using plasma from control women and from pregnant women, control women and women with toxemia of pregnancy, were performed. All experiments of the combined plasmas gave values equal to the sum of the values for the two plasmas assayed separately.

Table III summarizes the effect on the plasma ChE activity of the administration of 0.2 Gm. of Sodium Amytal twice daily to three normal pregnant patients. Two control plasma ChE determinations were made on each patient before Sodium Amytal was administered. The Student t test was applied to

*Less than 1 chance out of 1,744,000 that the difference in the means of the two groups could occur by chance.

†Less than 1 chance out of 1,438 that the difference in the means of the two groups could occur by chance.

the difference of the average of the 5 control determinations and of the average of the 10 determinations after administration of Sodium Amytal. The average of the ChE values after administering Sodium Amytal was 92.7 per cent of the control level. It was found that the means differed by a low level of significance.* The data indicate then that Sodium Amytal has a small but definite depressant effect on plasma ChE.

TABLE II. THE RESULTS OF A TYPICAL EXPERIMENT ASSAYING NORMAL PREGNANT PLASMA AND TOXEMIA OF PREGNANCY PLASMA SEPARATELY AND TOGETHER

WARBURG VESSEL	PATIENT	MILLILITERS OF PLASMA ASSAYED	ChE ACTIVITY CMM. CO ₂ PRODUCED/TEN MINUTES	
			EXPERIMENTAL	THEORETICAL
1	Normal Preg- nancy	0.1	44.9	
2	Toxemia of Pregnancy	0.1	29.9	
3	Normal Preg- nancy and Toxemia of Pregnancy	0.1 of each	74.1	74.8

TABLE III. THE EFFECT OF 0.2 GM. OF SODIUM AMYTAL TWICE A DAY ON PLASMA ChE ACTIVITY IN NORMAL PREGNANT WOMEN

DAYS	PATIENT		
	1	2	3
Before	41.1*	39.0	40.2
Before	42.5	39.4	
3	36.5	35.5	34.8
6	38.6		39.0
9	35.6		
12			39.0
14	42.1		
16	36.8		
19			37.2

*ChE activity expressed as c.mm. CO₂/ten minutes/0.1 ml. of heparinized plasma.

Comment

These data indicate that the ChE activity in heparinized plasma from women who are normally pregnant is significantly lower in activity than in nonpregnant, nonmenstruating, healthy, adult women; thus, confirming the observations of Zeller and associates² and others.^{3, 4, 5} Moreover, the data also show that the activity of ChE in plasma from patients with toxemia of pregnancy is significantly lower than plasma ChE activity for normal pregnancy. In the case of toxemia of pregnancy the difference is greater than could be expected from the effects of medicants such as Sodium Amytal. The study represents another link in our knowledge of the enzymatic changes during the toxemias of pregnancy.

Since the changes observed between the three groups is seemingly independent of the action of inhibitors or activators in the blood, some mention should be made of the changes in blood volume during pregnancy and of the origin of plasma ChE. Dieckmann and Wegner¹⁰ and others¹¹ observed a 25 per cent (or more) increase in plasma volume during pregnancy, accounting for the relative decrease during gestation in cellular elements and plasma proteins. It is possible that the decrease in plasma ChE observed during normal

*Less than 1 chance out of 20 that the difference in the means of the two groups could occur by chance.

pregnancy (20 per cent in this report) could be the result of hemodilution due to the increase in plasma volume.

On the other hand, many studies indicate that the liver is involved in the production of serum ChE. McArdle¹² and Kunkel and Ward¹³ found that in a majority of cases (79 per cent in McArdle's series) of various liver diseases, plasma ChE activities were below normal. Although Dieckmann¹⁴ states that there are no characteristic histologic changes in the liver during pregnancy, alterations in many of the functions of the liver, as determined by various tests, may occur. Krebs and Dieckmann¹⁵ and others^{16, 17, 18} have reported on liver-function tests during normal and toxemic pregnancy. A summation of these studies would indicate a depression with some tests during normal pregnancy which was more marked during toxemic pregnancy. The lower activity of plasma ChE reported in this study may represent an expression of altered hepatic function.

Page¹⁹ has suggested that placental dysfunction may be the source for the enzyme disturbances in the blood during toxemia of pregnancy. We have noted no difference between the beta-glucuronidase activity in placental homogenates of normal and toxemic placentas,²⁰ whereas the beta-glucuronidase activity of the plasma is increased.¹ Woodbury and co-workers²¹ have reported that the ChE activity of placentas from pre-eclamptic patients was greater than that of placentas from normal patients. What relationship lies between the latter finding and the lower ChE activity in toxemic plasma is not clear.

In this study considerable variation of plasma ChE was encountered among individuals. It is unlikely, therefore, that plasma ChE activity can be used as a laboratory guide for the diagnosis of pregnancy or toxemia of pregnancy. Similarly, no correlation could be made between the clinical severity of the toxemia and the degree of ChE depression. Experience gained during a previous enzymatic study¹ applies to the present report; namely, enzyme relationships during pregnancy and toxemia of pregnancy are physiological trends, not specific defects; they merely enlarge our understanding of basic metabolic changes.

Summary

ChE activity in plasma from normal adult nonmenstruating, nonpregnant women, from women during normal pregnancy, and from patients with toxemia of pregnancy was determined manometrically. Significant differences were observed among the three groups. This difference was independent of medication (Sodium Amytal), and could not be attributed to the effect of inhibitors or activators in the blood. The significance of these changes is discussed.

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STILLBIRTH AND NEONATAL MORTALITY IN A GENERAL HOSPITAL

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THE great reduction in maternal mortality brought about during the past fifteen years has provided the obstetrician with an opportunity to study the problem of stillbirth and neonatal mortality. Investigation and comparative studies are difficult and often of little value for there is no unanimity of opinion at present on the basic definitions of viability, prematurity, stillbirth, and the neonatal period. Even the Federal and State laws governing reportable births are not uniform.

The purpose of this study was to investigate the problem of fetal and neonatal mortality as it exists in a general hospital. In addition we hoped to develop a tentative pattern with precise definitions for subsequent analyses.

Material

The report is concerned with the three years extending from Jan. 1, 1947, to Jan. 1, 1950, and included all the products of gestation that have passed the 20th week. Fetuses of less than 28 weeks' gestation were considered previable, those of 28 to 38 weeks premature, and the remainder of full-term gestation. The neonatal period included the first ten days of life. During the interval studied there were 3,958 fetuses and infants beyond the 20th week of gestation delivered. There were 83 stillbirths, or a ratio of 21.4 per thousand live births. In 3,875 live births there were 91 neonatal deaths, or 2.3 per cent. The total fetal loss was 4.4 per cent but when corrected by the deduction of previable fetuses was only 2.05 per cent.

Investigation of the etiology of stillbirth necessitates analysis of the fetal deaths which occurred prior to or after the onset of labor and the apparent duration of pregnancy in each case.

Antepartum Deaths

There was a total of 83 stillbirths in infants of 20 weeks or more of gestation; 37 of these occurred in premature or term infants. The cause of death in 48.6 per cent could be attributed to uncontrollable dysfunction of the cord, placenta, or fetal anomalies. In 16 cases, or 40.5 per cent, no cause of death could be definitely ascertained; 11 died prior to the onset of labor and the other 5 deaths occurred in spontaneous parturition. The 2 term fetuses which perished intrapartum died as the result of forceps application. The deaths attributed to maternal causes were due to one case of pre-existing chronic glomerulonephritis and one case of diabetes mellitus.

TABLE I. TOTAL FETAL LOSS

YEAR	STILLBIRTHS					NEONATAL DEATHS							TOTAL FETAL LOSS TRUE FOR VIABLE FETUSES
	TOTAL LIVE BIRTHS	TOTAL			RATIO PER 1,000 LIVE BIRTHS	TRUE RATIO PER 1,000 LIVE BIRTHS	TOTAL			PER CENT OF LIVE BIRTHS	TRUE PER CENT OF LIVE BIRTHS		
		AT TERM	28 WEEKS AND OVER	20 WEEKS AND OVER			AT TERM	28 WEEKS AND OVER	20 WEEKS AND OVER				
1947	1,387	10	3	15	20.1	9.3	9	9	8	1.8	1.2	3.8	2.13
1948	1,207	6	10	9	20.7	10.7	12	4	11	2.2	1.3	4.2	1.37
1949	1,281	3	5	22	23.4	6.2	3	8	27	2.9	.85	5.2	1.47
Total	3,875	19	18	46	21.4	9.5	24	21	46	2.3	1.1	4.4	2.05

TABLE II. ANALYSIS OF VIABLE STILLBORN FETUSES AS TO TIME OF OCCURRENCE, GESTATION, AND CAUSE

TIME OF OCCURRENCE	GESTATION	NUMBER OF DEATHS DUE TO CAUSES IN						TOTAL
		CORD	PLA-CENTA	FETUS	MOTHER	UN-KNOWN	FORCEPS APPLI-CATION	
Ante-Partum	Term		1	1	1	4		7
	Premature		3	3		7		13
Intra-Partum	Term	3	1	1	1	4	2	12
	Premature	2	1	2				5
Total		5	6	7	2	15	2	37

Fetal anoxia is the basic cause in almost all fetal deaths ante partum and the precipitating lesion can be either intrinsic or extrinsic.

(a) Intrinsic causes are those related to conditions of the fetus, cord, or placenta which initiate anoxia.

(b) Extrinsic causes are those basically related to the maternal organism and attributable to

(1) Maternal oxygen deficit as manifest in diseases of the blood, heart, and lungs.

(2) Transmission of toxic substances from the mother.²

Intrapartum Deaths

Dystocia per se will produce its effect as a cause of stillbirth and neonatal death. However, the treatment employed to overcome an intrapartum complication, which by itself would not have been fatal, is all too frequently the lethal factor. The obstetrician has been made aware of the potential dangers of interference not only to the mother but to the unborn child. The modern woman demands that she emerge from pregnancy and labor without serious damage to herself and that she be delivered of a normal, healthy child. There are many types of fetal injury that can occur intrapartum but that most commonly fatal is intracranial hemorrhage. This accident can and does occur in spontaneous deliveries. However, except in cases of premature delivery, it is largely preventable. Intrapartum fetal loss can be decreased only through proper choice of operative procedure and skillful application of it at the appropriate time.

TABLE III. NEONATAL DEATHS

CAUSE OF DEATH (AUTOPSY DONE IN 28 CASES)	PREMATURE	TERM	TOTAL
Pulmonary pathologic changes	7	8	15
Congenital malformations (incompatible with life)	2	6	8
Erythroblastosis	3	1	4
Unknown (no autopsy nor significant clinical finding)	8	1	9
Status thymicolymphaticus (autopsy)		1	1
Birth injury (intracranial hemorrhage)	1	7	8
Type of delivery:			
Spontaneous vertex	3		
Breech (manual aid)	1		
Low forceps	2		
Midforceps	1		
Internal podalic version and breech extraction	1		
	21	24	45

Fetal narcosis, anoxia, and subsequent death occur far too frequently from the ill-advised administration of analgesics, hypnotics, and sedatives in an attempt to control the pain of childbirth. Hingson, Lull, Schmitz^{3, 4} and others

have clearly demonstrated that all forms of regional nerve anesthesia produce a marked reduction in fetal loss by avoiding prolonged maternal narcosis during labor and general anesthesia for delivery.

Comment

This study confirms the findings of other investigators that the chief causes of neonatal death are pulmonary pathologic changes fetal anomalies, and birth injury, as well as the fact that premature infants make up almost 50 per cent of the neonatal loss. Congenital anomalies are not preventable in the light of present knowledge and expert obstetrical care will limit the deaths due to dystocia. There remains the problem of salvage in infants born prematurely, for they constitute the greatest single cause of neonatal death. The cause of premature labor in most cases is just as obscure as the cause of term labor. Premature labor once established cannot be arrested but if the obstetrician will learn and accept prerequisites of good management in such cases he will be rewarded by a larger number of healthier infants.

Conclusions

An attempt must be made to create uniform definitions of stillbirth, viability, prematurity, and the neonatal period which will be accepted by all hospitals.

Stillbirth.—The National Office of Vital Statistics has defined stillbirth as the birth of a fetus or infant which has reached the twentieth week of gestation but which has no heartbeat, does not breathe, nor show any movement of voluntary muscle.

Viability.—The criteria of viability most commonly used are (1) the termination of uterogestation prior to the end of the 28th week; (2) a body weight of less than 1,000 grams; (3) a crown-heel length of less than 37 cm.

None of these can be accepted without reservation. Calculation of the duration of gestation from the last menses is subject to many errors and the size of the fetus is modified by race, hereditary characteristics, and diseases of the mother. However, fetal survival is directly related to the birth weight and if this is correlated with the other measurements, errors will be kept at a minimum.

Prematurity.—The standard of prematurity as set forth by the American Academy of Pediatrics is "every living child whose weight at birth is 2,500 grams or less." This is widely accepted and should be adopted as a basic definition by all hospitals with maternity services.

Neonatal Period.—Infant death directly attributable to pregnancy or the processes of labor will in almost all cases occur during the first seven days of neonatal life. The end of the seventh day should be considered the termination of the neonatal period.

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AN EVALUATION OF BREECH PRESENTATION AND VAGINAL DELIVERY

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AT THE Cincinnati General Hospital from 1938 to 1947, there were 22,935 deliveries, of which 888 were breech presentation, an incidence of 3.9 per cent. Of the 888 cases, there were 495 full-term breech deliveries of mothers without prenatal or intranatal complications. There are no private cases and there is no selection of cases; all deliveries are conducted by residents and interns under staff supervision.

Since we are considering only vaginal delivery, four cases of cesarean section will be eliminated from this survey. Of the remaining 884 breech deliveries, 607 were frank breech, 87 were single footling, and 190 were double footling presentations. There were two maternal deaths which will be discussed briefly later. The uncorrected and corrected fetal mortality for each type is listed in Table I. This includes births of all infants of 1,000 grams and over. We corrected for maceration, weight under 1,500 grams, and congenital anomalies incompatible with life.

TABLE I. TOTAL BREECH PRESENTATIONS, 884

	FRANK	SINGLE FOOTLING	DOUBLE FOOTLING
No. of cases	607	87	190
Uncorrected fetal mortality	16.6%	19%	11.4%
Corrected fetal mortality	11.5%	14.9%	5.7%

There were 273 primiparas and 611 multiparas, the ratio being about 1:2. It is common belief that the primiparous patients with breech presentation have a higher fetal mortality. This credence is not borne out by the figures ascertained in this survey, as can be seen in Table II.

TABLE II. FETAL MORTALITY ACCORDING TO PARITY

	PRIMIPARAS	MULTIPARAS	TOTAL BREECHES
No. of cases	273	611	884
Uncorrected fetal mortality	12.5%	15.8%	15%
Corrected fetal mortality	8%	10.7%	9.9%

Authors differ as to the preferred method of delivery in breech presentation. Manual aid, as defined by DeLee and Greenhill,¹ is spontaneous delivery of the breech to the umbilicus, then extraction of the body, shoulders, and head under deep anesthesia. Stander² advises no interference, even when the umbilicus is reached. Irving and Goethals³ and Titus⁴ advise extraction of all breech presentations after complete dilation and paralysis of the cervix. Piper and Backman⁵ advocate the use of forceps for the delivery of all aftercoming heads. Most authors recommend the use of x-ray in all breech presentations whether abdominal or vaginal delivery is contemplated.^{6, 9, 10, 11, 12} Most authors are in

full agreement that all manipulation should be done under full surgical anesthesia and the baby delivered in the manner advised by Potter.⁶

TABLE III. FETAL MORTALITY RATES BY METHOD OF DELIVERY (884)

	SPONTANE- OUS	AIDED	EXTRAC- TION	TOTAL 1938-1947	TOTAL 1947
No. of cases	348	348	188	884	101
Uncorrected fetal mortality	19%	12.9%	15.9%	15.09%	10.2%
Corrected fetal mortality	12.3%	8.5%	11.2%	9.9%	3.6%

Prior to January, 1947, we allowed all breech presentations to deliver spontaneously to the umbilicus under light inhalation anesthesia and aided by a generous episiotomy. At this point, the anesthetic was deepened and extraction of the infant was completed. In January, 1947, in addition to inhalation anesthesia, we began using pudendal block (1 per cent procaine) to produce perineal relaxation. The combined anesthesia allowed easier spontaneous delivery to the umbilicus; then the patient was put to sleep and the delivery was completed by manual aid. With combined anesthesia, when extraction becomes necessary, the operator is aided in all intravaginal and intrauterine manipulations.

The 1947 breech deliveries are noted and there is a decided improvement in corrected fetal mortality. This group is a small one, and in five years another study should be made to see if the improvement continues.

Out of the 884 cases, there were 495 patients with no prenatal or intranatal complications which would influence the neonatal mortality. This group was subdivided into the various types of deliveries, and the results are shown in Table IV.

TABLE IV. FULL-TERM BREECHES WITH NO MATERNAL COMPLICATIONS (495)

	FRANK			SINGLE FOOTLING			DOUBLE FOOTLING		
	SPON- TANE- OUS	AIDED	EX- TRAC- TION	SPON- TANE- OUS	AIDED	EX- TRAC- TION	SPON- TANE- OUS	AIDED	EX- TRAC- TION
No. of cases	122	145	75	9	26	7	33	62	16
Uncorrected fetal mortality	3.3%	5.5%	15%	22.2%	15.4%	14%	3%	6.4%	0
Corrected fetal mortality	1.6%	1.4%	9.4%	22.2%	11.5%	14%	3%	4.6%	0
Total	3.21%			14.93%			3.61%		

In this small group, frank and double footling presentation show a decided improvement in fetal mortality; whereas, single footling presentation shows a constant high fetal mortality. This is persistent in both groups. The factors governing this constant high mortality are poor dilatation and the frequency of early delivery through an undilated cervix.

Fetal anomalies were infrequent. There were 3 anencephalic monsters, 3 hydrocephalic monsters, and 4 cases of spina bifida. There were 8 macerated fetuses. There were 4 cases of prolapsed cord, and 5 cases of polyhydramnios.

The incidence of cesarean section was 0.4 per cent. This is extremely low, and review of the history charts indicates more should have been done.

TABLE V. PUERPERAL MORBIDITY ACCORDING TO METHOD OF DELIVERY

METHOD OF DELIVERY	RATE OF MORBIDITY
Average morbidity	5.9%
Spontaneous	4.3%
Aided	4.9%
Extraction	15.3%

Puerperal morbidity for the 884 cases was 5.9 per cent. This is low when compared with that of other teaching institutions.⁷ Extraction has the highest incidence of morbidity.

Induction of labor influences morbidity, and bag induction carries the highest incidence.

TABLE VI. MORBIDITY OF BREECH DELIVERY ACCORDING TO ONSET OF LABOR

TYPE OF LABOR ONSET		RATE OF MORBIDITY
Spontaneous	(837)	5.4%
Induced	(47)	8.7%
Medical		16.6%
Bag		5.9%
Average morbidity		

There were two maternal deaths in this series. One patient was a pre-eclamptic with a fetopelvic disproportion due to a 12 pound infant. She died of septicemia. The other was also a pre-eclamptic with an abruptio placentae who died of shock from postpartum hemorrhage. Both were delivered by breech extraction—obvious mismanagement. Each should have been delivered by cesarean section.

Comment

In 884 cases of breech delivery per vaginam at the Cincinnati General Hospital during the past ten years, the frank breech presentation was most often encountered. The fetal mortality in delivery in this presentation is high because many cases showed fetopelvic disproportion, and extractions were done after prolonged labor when marked fetal distress was present. The single footling breech presentation carries an even higher fetal mortality, resulting as it often does in early rupture of the membranes, premature labor, prolapse of the cord, and attempted early delivery with insufficient dilatation. The double footling breech is a better dilating mechanism and complete dilatation occurs more often with this presentation. The legs acting as splints help protect the cord if it should prolapse.

A significant finding in this survey is that the multiparas had a higher fetal death rate than the primiparas. We are sure that a part of the high fetal mortality is due to larger babies, failure to recognize early fetal distress, and too much haste in delivery. We attribute this to undiagnosed presentation resulting from inadequate observation during labor. In primiparas the converse is true.

Combined anesthesia is a definite aid in all breech presentations, giving better perineal and uterine relaxation. This is a necessity in any operative procedure, and definitely facilitates breech extraction.

The average morbidity of 5.9 per cent for breech deliveries is much less than our entire service morbidity of 7.84 per cent as reported by Pierce in 1948. However, where intrauterine manipulation occurs, we found a definite increase in morbidity with breech extraction having a 15.3 per cent and operative induction of labor having a 16.6 per cent incidence of morbidity. These are shown in Tables V and VI.

Since penicillin is now more readily available, it is used prophylactically in these cases in which the membranes have ruptured, and where intrauterine manipulation or surgical termination is contemplated.

Conclusions

1. Breech delivery carries a high fetal mortality. This can be improved by careful examination for disproportion, by closer observation of the patient in labor, and by unhastened delivery.

2. A frank breech should be delivered spontaneously or by manual aid, while a single footling should be delivered by manual aid only.

3. Breech extraction should be reserved for those cases in which complete dilatation and paralysis of the cervix exist. In this series, in the double footling presentation, these prerequisites for extraction were always found.

4. Combined anesthesia facilitates intravaginal and intrauterine manipulation, and when possible should be used routinely in delivery in all breech presentations.

5. Forceps delivery of the aftercoming head is indicated if there is any difficulty in its manual extraction.

6. Vaginal manipulation and induction of labor is followed by an increase in puerperal morbidity.

7. All cases of breech presentation should receive benefit of x-ray whether abdominal or pelvic delivery is anticipated.

8. Cesarean section should be resorted to in the case of actual or relative disproportion and in the elderly primigravida.

9. Beware the treacherous multipara.

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2500 MELROSE AVENUE

THE USE OF HYALURONIDASE IN PUDENDAL BLOCK

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IN VIEW of the recent publicity given to Dr. Grantly Dick Read's method of "natural" childbirth, much consideration was given by the author to pudendal block as an adjunct to such a method and to it as the procedure of choice in the usual uncomplicated delivery. The advantages and limitations of pudendal block have been described again and again, so, except for remarks which are pertinent to the author's investigation of the use of hyaluronidase* in obstetrics, the arguments regarding such an anesthetic will not be reopened.

It is obvious that during labor the uterine contractions are painful to a varying degree. It is fairly well established that the degree of pain, labor being normal, is dependent upon the mental "make-up" of the patient—the so-called "pain threshold." The course of labor as perceived by the patient will be affected only by her mental attitude and the use of analgesics and/or amnesics, not by the anesthetic to be administered. It is further acknowledged that the expulsion stage and the concomitant distention of the vulva during childbirth is probably the most painful portion of labor. If this is true it is only necessary then to insure that the vulva, perineum, and the structures contained therein are not the source of painful stimuli during delivery. Abolition of such stimuli can easily be accomplished by means of pudendal block.

From a purely physical standpoint, physicians object to the use of local anesthetics in obstetrics for the following reasons:

1. They dislike distention of the tissues by the anesthetic solution.
2. Many assume that special skill is necessary for proper administration.
3. They feel that such an anesthetic would not completely anesthetize and relax the tissues involved.
4. Some object to the latent period before the anesthetic becomes completely effective.

From a standpoint other than physical, many physicians have been reluctant to use a local anesthetic because the patient has been conditioned, through various sources, to expect much pain and discomfort from childbirth unless she is either asleep or under the influence of a spinal anesthetic; this concept has certainly been fostered by many obstetricians, and no doubt they dare not attempt to change lest the patient go elsewhere for her obstetrical care. If physicians were to inculcate in the minds of their patients that a general anesthetic is usually unnecessary and not to be expected, the attitude on the part of the patients would change. The added risk and expense of a general or spinal

*Hydase, lyophilized hyaluronidase, generously supplied by Wyeth Incorporated, Philadelphia, Pa.

anesthetic are not being considered in this paper; it is merely pointed out that pudendal block can be equally as effective as other types of anesthetics when the delivery is normal. On an obstetrical service wherein this procedure is practiced, the patients expect nothing more and are well satisfied.

In order to overcome the objections to local anesthesia, as listed above, hyaluronidase was added to the anesthetic solution. Kirby and Looby¹ state that when hyaluronidase and epinephrine are added to a solution of procaine and this solution injected into the skin, the area anesthetized is increased by about 40 per cent over the area anesthetized by procaine alone. They further state the duration of anesthesia to be equal in both cases. According to Hechter, Dopkeen and Yudell,² hyaluronidase has no effect on the spread of localized infection provided it is not injected into the affected area. According to them, hyaluronidase can penetrate a fibrin barrier only if it is introduced directly into it; otherwise it diffuses around such an obstruction, following the path of least resistance. It is not necessary to give a detailed account of the duration and area of anesthetized skin with varying solutions of procaine, hyaluronidase, and epinephrine and to compare it to the use of procaine alone. This has been adequately done by Kirby, Eckenhoff, and Looby¹.

Procedure

The solution used was 50 c.c. of 0.5 per cent procaine, 1 c.c. of 1:1,000 epinephrine, and 2 ampules of Hydase (each containing at least 150 turbidity reducing units). From this stock solution an average of 30 to 40 c.c. was used per patient. The technique for injection was that described in Beck's *Obstetrical Practice*.³ Five c.c. were deposited bilaterally in the vicinity of the pudendal nerve before it entered Alcock's canal; 5 c.c. were deposited bilaterally superior and lateral to the clitoris in order to block the terminal branches of the ilio-guinal nerve; and 5 c.c. were deposited bilaterally just posterior and medial to the ischial tuberosity to anesthetize the lateral cutaneous branch of the femoral nerve.

Complete anesthesia and relaxation of the vulva and perineum were determined by lack of response to such stimuli as pin prick, grasping the tissue with Allis forceps, etc., inability to contract the anal sphincter and relaxation of all muscles of the perineum, including the anterior pillars of the levator ani.

It is important to note that the delivery of each baby was done only when the patient was not having a uterine contraction. Relaxation and cooperation on the part of the patient are, of course, necessary; extreme gentleness on the part of the physician is mandatory.

Results

In a series of fifty cases, including both primigravidas and multigravidas, there was but one failure of complete anesthesia and relaxation of the perineum; in this case the patient stated afterward she felt pain on one side of the vulva during delivery. One abscess resulted because the solution was unknowingly injected into a previously infected area. Low forceps and episiotomies were used as indicated. The incidence of low forceps was markedly reduced because of the expulsive efforts on the part of the patient, when these efforts were requested by the physician. Each patient was carefully questioned after delivery as to whether or not pain was felt and with the exception noted above, the answer was uniformly "no." In many instances the mother was not aware that the child had been born until she heard its cry.

The anesthetic injected spread very rapidly. The distance it spread was proportional to the force with which it was injected. Because of its marked

spreading ability it is evident that it was not necessary to deposit the anesthetic directly at the site of the nerve. For the same reason, adjacent tissues which were not supplied by the nerve injected were also anesthetized. Because of the rapid diffusion of the solution it was only natural that induction of anesthesia was much more rapid than when procaine alone was used. The duration of anesthesia was equal to that of procaine alone. There was no distention of tissue anywhere. Because of the properties of hyaluronidase, its use is particularly indicated in pudendal block in order to obviate the possibility of some anatomical variation in the course of the nerve one wishes to anesthetize. Although local infiltration in the perineum is unnecessary with the technique described above, if it is used, the injected solution disperses in a matter of minutes. A wide area of anesthetized tissue is left which appears and feels to the examining finger as though no solution had been injected.

Summary

The use of hyaluronidase is found to be a safe and simple method for increasing the efficiency of pudendal block in obstetrics and for overcoming many of the objections to this type of obstetrical anesthetic.

Hyaluronidase increases the efficiency of pudendal block because:

1. There is no tissue distention from the solution.
2. Onset of anesthesia is rapid.
3. Anesthesia extends into adjacent tissues.
4. It is not necessary to deposit the anesthetic at the nerve site itself.
5. The vulva and perineum are completely anesthetized and relaxed.
6. A minimum amount of anesthetic produces the desired results.
7. Duration of anesthesia is sufficient for the normal delivery.

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2125 ARLINGTON AVENUE.

PROPHYLACTIC APPENDECTOMY IN GYNECOLOGICAL SURGERY

A Review of 532 Cases

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PATHOLOGICAL reports of catarrhal appendicitis and early acute appendicitis are made, from time to time, on appendices removed incidental to pelvic surgery on the female reproductive organs. The following study was undertaken in order to determine the incidence of appendicitis and thereby to evaluate the necessity of performance of an appendectomy during such operations.

Material

The material comprises a study of the case histories and pathological reports of 532 women patients who had the appendices removed during the course of pelvic surgical operations at the St. Joseph's Hospital, Milwaukee, Wis., for the years 1946 to 1949. In all of these patients, the abdomen was opened primarily to remove or correct a disease process of the female reproductive organs and the appendix was extirpated secondarily as a routine measure. The presenting symptoms and underlying pathologic conditions in these patients were primarily gynecological in nature, or thought to be so by their attending surgeon, as noted in the pre- and postoperative diagnosis. Some of the most common complaints in the patients were: pain, discomfort, or pressure sensation in the lower abdomen, dysmenorrhea, menorrhagia, metrorrhagia, sterility, presence of a palpable mass, and prolapse of the uterus. Lower abdominal pain of varying type and degree was a frequent complaint in many of the patients. A number of them had an exploratory laparotomy because a mass was palpable on bimanual pelvic examination in either the right or left adnexa or both.

Analysis of the 532 cases, shows that there were 277 hysterectomies with salpingo-oophorectomy. The majority of these were total hysterectomies with removal of the bilateral adnexal organs, and the others were subtotal hysterectomies with either unilateral or bilateral salpingo-oophorectomy. Hysterectomy with salpingectomy was performed in 4 cases, and total or subtotal hysterectomy in 59 cases. There were 72 cases of salpingo-oophorectomy (unilateral or bilateral), 11 cases of salpingectomy and 59 cases of oophorectomy. The adnexal organs were removed for various pathological conditions such as cysts, tumors, carcinoma, endometriosis, tubal pregnancy, salpingitis, pyosalpinx, hydrosalpinx, and oophoritis. The appendix was removed together with ruptured tubal pregnancy in 11 cases. Other surgical procedures included: myomectomy 7 cases, uterine suspension 41 cases, and freeing of pelvic adhesions 2 cases.

Analysis of Pathological Examination of the 532 Appendices

Acute inflammation was present in 56 (10.5 per cent) of the 532 appendices removed during pelvic surgery. Of these, 51 cases were diagnosed by the path-

ologist as catarrhal appendicitis in which the inflammation was confined to the mucosa, 2 as subacute appendicitis, and 3 as early acute appendicitis in which the inflammation was diffuse in character involving not only the mucosa but also the submucosa and muscularis. Of the 51 cases of catarrhal appendicitis, 20 were associated with hysterectomy with salpingo-oophorectomy, 9 with salpingo-oophorectomy, 5 with uterine suspension, 7 each with oophorectomy and with hysterectomy, 2 with salpingectomy, and 1 with freeing of pelvic adhesions. It is more important to note that while the number of appendices with catarrhal inflammation varied with the type of gynecological surgery, the incidence distribution was fairly constant when computed on the basis of number of appendices removed with each type of surgery—hysterectomy with salpingo-oophorectomy 7.2 per cent, salpingo-oophorectomy 12.5 per cent, oophorectomy 11.9 per cent, hysterectomy 11.9 per cent, uterine suspension 12.2 per cent, and salpingectomy 18.2 per cent. Among the 11 appendices removed with ruptured tubal pregnancy, 3 showed catarrhal inflammation of the mucosa, in addition to the usual periappendiceal inflammation.

Periappendicitis, in itself, is of no clinical significance, for it merely represents an inflammation of the serosa, most commonly an extension of an acute inflammatory process from an adjacent organ. There were a total of 34 cases of periappendicitis, of which the greatest number were associated with salpingo-oophorectomies. Five of them, in addition to the periappendicitis, showed acute catarrhal inflammation of the mucosa.

The predisposing factor in the causation of the appendicitis in all the cases was obstruction of the lumen, either by a fecalith or by marked narrowing of the lumen associated with submucosal fibrosis or lymphoid hyperplasia, producing partial or complete obstruction by the presence of inspissated feces. In the group of catarrhal appendicitis cases, obstruction was caused by fecalith in 18 cases, by submucosal fibrosis in 30 cases, by lymphoid hyperplasia in 2 cases, and by buckshot in 1 case. In those with subacute appendicitis, submucosal fibrosis was the primary cause of obstruction; and in those with acute appendicitis, submucosal fibrosis in one case and fecalith in 2 cases. In the case of acute appendicitis associated with submucosal fibrosis, there was pinpoint narrowing of the lumen at the base due to fibrotic change in the submucosa at this site.

In 114 appendices (21.4 per cent), no lesion was noted. Submucosal fibrosis was present in 174 cases (32.7 per cent), fibrosis with obliteration of the lumen in 73 cases (13.7 per cent), lymphoid hyperplasia in 20 cases (3.8 per cent), chronic appendicitis in 2 cases (0.4 per cent), *Enterobius vermicularis* infestation in 1 case (0.2 per cent), fecalith without inflammation in 53 cases (10.0 per cent), mucocoele in 2 cases (0.4 per cent), and others such as melanosis and endometriosis, 3 cases (0.6 per cent).

Comment

A relatively high incidence of acute inflammation is found in appendices removed incidental to pelvic laparotomies. Of the 532 cases, 9.6 per cent were reported as catarrhal appendicitis and 0.9 per cent as subacute and early acute appendicitis. There is little question about the seriousness of the latter type of inflammation. The clinical manifestations of the catarrhal type of appendicitis where the inflammation is confined to the mucosa are more difficult to evaluate. No doubt such a lesion can produce dull, vague pain in the lower abdomen and could account for the symptoms in some of the patients. In such appendices, there exists the danger of extension of the inflammatory process from the mucosa to the other layers of the wall resulting in acute diffuse appendicitis.

Fecalith, which is one of the most important predisposing causes of acute appendicitis, was present in 10 per cent of the cases, excluding those with acute inflammation. Here again, how many of them would produce acute appendicitis if not surgically removed is a matter of conjecture. Without doubt, appendectomy in this type of case is a definite prophylaxis against the future development of acute appendicitis.

The occurrence of submucosal fibrosis and lymphoid hyperplasia cannot be disregarded, since the predisposing factor in the development of acute appendicitis is obstruction, independent of its cause.¹ These conditions can produce marked narrowing of the lumen, thus enabling tiny particles of inspissated feces to complete the obstruction. Under ordinary conditions, submucosal fibrosis with obliteration of the lumen begins at the tip of the appendix and gradually progresses toward the base. In some cases, the obliterative process may begin in other areas. If fibrosis and constriction of the lumen take place at the base of the appendix, the development of an acute appendicitis is inevitable.

Chronic appendicitis has been the subject of much controversy because of the difficulty in correlating the clinical symptoms attributable to the appendix, with the microscopic findings. Clinically, the term has been used to denote a recurrent type of pain in the right lower quadrant of the abdomen due to intermittent attacks of acute appendicitis. From the histopathological standpoint, a diagnosis of chronic appendicitis is seldom made due to the lack of cellular reaction as is characteristic of chronic inflammation elsewhere in the body. Many of the recurrent attacks of so-called chronic appendicitis are probably due to episodes of intermittent obstruction of the lumen by fecalith, submucosal fibrosis, and kinks, with the development of a catarrhal, subacute, or an acute type of inflammation. In our review, there were two cases diagnosed as chronic appendicitis.

Clinically, the differential diagnosis between appendiceal and adnexal lesions may be very difficult at times, for the symptomatology and physical findings frequently overlap, and not infrequently both lesions co-exist. To make the differential diagnosis more difficult, appendicitis is atypical in from 25 to 50 per cent of the cases.² Even with the abdomen opened, an inflammation of the appendix, especially of the catarrhal type, can be overlooked in cursory examination when the operator's mind is centered on the pelvic pathologic conditions. Furthermore, a periappendicitis, secondary to inflammation of the adnexal organ, or congestion of the periappendiceal vessels produced by excessive manipulation of the bowel, cannot be easily differentiated from a true catarrhal or an early acute appendicitis. The two conditions may co-exist, and failure to remove an appendix with a diagnosis of periappendicitis may be tragic.

The fact that the appendix may produce future trouble if allowed to remain and that it can be removed during pelvic surgery with little added risk indicates that it should be removed routinely whenever the opportunity presents itself. In this review of 532 cases of prophylactic appendectomy, there was only one death. This patient, who had a total hysterectomy and salpingo-oophorectomy, died on the nineteenth postoperative day from hemorrhage, peritonitis, and pulmonary embolism. According to the autopsy report, the peritonitis was attributable to the hysterectomy.

Summary and Conclusions

1. Five hundred thirty-two appendices removed incidental to pelvic surgery in women are reviewed from the histopathological standpoint. Ten and one-half per cent of them showed acute inflammation, of which 9.6 per cent was

catarrhal in nature with the inflammation confined to the mucosa, and 0.9 per cent subacute and acute with a diffuse type of inflammation.

Ten per cent of the noninflamed appendices were found to contain a fecalith which is one of the most important and frequent predisposing causes of acute appendicitis.

The incidence of the various types of lesions in the appendices is discussed from the viewpoint of histopathogenesis of acute appendicitis.

2. Catarrhal appendicitis, as well as subacute and early acute appendicitis, can easily be overlooked even with the abdomen opened in pelvic surgery.

3. The appendix should be removed routinely in pelvic surgery whenever it is accessible.

4. In this series of cases, there were no deaths directly attributable to prophylactic appendectomy.

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5000 WEST CHAMBERS STREET

PLASMA PROTHROMBIN DURING PREGNANCY AND THE PUERPERIUM

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VARIOUS workers have disagreed as to the behavior of plasma prothrombin during pregnancy. Thordarson,^{1, 2} Schönheyder and Olsen,³ Adams,⁴ and Marti and Fernandez⁵ found elevations as compared to the levels of nonpregnant women. Javert and Macri,⁶ however, found normal to less than normal figures and Javert and Stander⁷ suggested a prothrombin deficiency might be a factor in spontaneous and habitual abortion. Such conflicting data are difficult to explain though differences in techniques for measuring prothrombin may be in part responsible for such disagreement.

It is the purpose of this paper to report data on the behavior of the plasma prothrombin in 54 pregnant women studied from as early as the fifth week of pregnancy to as late as the tenth week following delivery.

Methods

The two-stage prothrombin assay of Warner, Brinkhous, and Smith⁸ was used throughout the study. The work was carried out during 1939 and 1940 prior to the discovery of the prothrombin accelerator factor (Factor V,⁹ Ac-Globulin,¹⁰ labile factor¹¹) and this variable had not as yet been rendered constant in the procedure. It should be pointed out that variations in this factor during pregnancy cannot be ruled out as a significant influence in the results obtained. In that the conversion of prothrombin to thrombin takes place in a separate and distinct phase from the conversion of fibrinogen to fibrin, variations in the accelerator factor are less of an influence in the two-stage technique than in the various one-stage methods.

Range of Study

Cases were selected from the outpatient clinic of the Presbyterian Hospital and range in time from the fifth week of pregnancy to the tenth week of the puerperium. Twenty-eight of the cases were brought into the study by the twentieth week or earlier, the remaining twenty-six cases being started in the second half of pregnancy. An attempt was made to obtain a determination at intervals of four weeks during the first eight months and at weekly intervals in the last month. Following delivery, levels were taken as nearly as possible on the first, second, and third days and then every second day until the patient left the hospital. Thereafter, determinations were spotty, a total of seventy-eight being obtained on twenty-one of the fifty-four patients between the eighth day and the tenth week post partum. During the entire study a total of 617

levels was taken, making an average of 11 per patient. Thirty of the patients whose prothrombin levels were below 100 per cent were given menadione (vitamin K) in doses varying from 3 to 6 mg. daily to determine its effect on such levels. It was started as early as the ninth week of pregnancy and was continued to term.

Most of the patients received ethylene and oxygen anesthesia during labor and Nembutal and/or Seconal up to 3 grains of each during the immediate pre- and postpartum stages. Morphine sulfate, Dilaudid, Pantopon and scopolamine were used in scattered dosages and in 10 cases quinine was used to induce labor.

Results

Of the 54 patients, 44 at one time or another had a prothrombin level above 110 per cent, 23 had levels above 120 per cent, 10 above 130 per cent, 3 above 140 per cent, and 2 were above 150 per cent. The highest level recorded was 174 per cent, this level being found in the thirteenth week of pregnancy. In general, the levels were slightly lower in the first trimester, tended to rise during the last six months and fell slightly in the last week before delivery. Forty-four patients followed this pattern. Forty patients showed a rise following delivery, 20 of these showing it the first day, 15 the second day, 3 the third, and 1 each the fourth and fifth days. This elevation persisted in most instances through the eighth or ninth day when most of the patients left the hospital. Of 21 patients studied after the second week post partum (representing a total of 78 determinations), 20 showed levels appreciably lower than those during pregnancy and the first week following delivery. Three who had levels as high as 149, 174, and 150 during pregnancy had values 112, 132, and 113, respectively, at the sixth week post partum. They may have had high levels normally though determinations of 132 per cent are rare. All other patients studied had levels of 100 per cent or less by the sixth week of the puerperium. There was no observable uniform effect on the prothrombin levels of those patients given vitamin K. The same held true with respect to the various drugs given during labor and the puerperium.

Comment

With the method used in this study prothrombin levels of above 110 per cent in the healthy adult human being are rare. Eighty-one per cent of the 54 patients in this study had a prothrombin at some time during pregnancy of 110 per cent or above. Our findings are in line then with those of investigators who found, in general, an elevation of the plasma prothrombin during pregnancy. It is of interest, however, to note that if the data of 24 of the patients who received no menadione be analyzed statistically it cannot be definitely concluded from such data that pregnancy is accompanied by a rise in plasma prothrombin. The defect in such a conclusion is that prothrombin levels were not obtained in these cases before pregnancy began or some months after it was terminated. In this connection, one patient, a nurse whose plasma was used frequently as a normal control, one day showed a result considerably higher than that of other controls. Since her prothrombin level had theretofore been remarkably constant, she was questioned as to the possibility of pregnancy and it developed she was at that time in her fifth week of gestation. Her prothrombin remained elevated throughout pregnancy and the immediate puerperium and has since returned to normal.

The reason for an elevated prothrombin during pregnancy is not clear. It might be reasonable to assume that it is a part of a protective mechanism against bleeding during this period.

Summary

In 54 women the plasma prothrombin was studied from as early as the fifth week of pregnancy to the tenth week following delivery. Forty-four, or 81 per cent, at some time during pregnancy had a prothrombin of 110 per cent or above. In general, the levels were slightly lower in the first trimester, tended to rise during the last six months, and fell slightly in the last week before delivery. There was a tendency to rise during the first week of the puerperium and to fall gradually toward normal during the following five weeks.

We wish to acknowledge valuable technical assistance given during this study by Miss E. A. Pearl.

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55 EAST WASHINGTON STREET

CURARE WITH GENERAL ANESTHESIA FOR VAGINAL DELIVERIES

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LAST August, with some trepidation, we used curare as an adjuvant to obstetric anesthesia for the first time. The reason for our disquietude was that we had not heard of its being used for vaginal delivery, nor had we read any such reports after a rather extensive coverage of the literature. There had been a few articles, particularly in the British literature, of the use of curare in cesarean section,¹ and we had used it rather extensively on the surgical services. The determining factor in our employment of this most useful drug was an article by Harroun and Fisher.² In this report it was definitely proved the drug did not pass the placental barrier nor did it inhibit normal postpartum contractions. Also, Doan and Huston³ used curare to soften convulsions when giving electric shock to patients suffering from depression during pregnancy. It was the fear of the probability of its entering the fetal circulation that had kept us from using curare sooner. We had demonstrated that it had no effect on dilatation of the cervix in deliveries of nonviable fetuses.⁴

Curare, although its history stretches back many centuries, has been considered and thought of only as a poison until the past few years. However, Brodie in 1811 suggested it as a cure for tetanus.⁵ In anesthesia Griffith and Johnson pioneered the use of curare as an adjuvant to anesthesia, reporting their work in 1942.⁶ Cullen has reported on a large series of patients.⁷

The exact action of the drug on muscular action is not known. McIntyre⁸ says, "a satisfactory theory cannot be forthcoming until the *modus operandi* of muscle excitation is fully explored, established, and agreed upon." He believes the most probable mechanism is one in which the normal role of acetylcholine is inhibited by the presence of curare at its point of action in the muscle.

Quiet often in delivery it is necessary to put the patient under deep or surgical anesthesia in order to relax the perineum. In fact, sometimes a spastic, rigid perineum or spastic levators can prevent the successful termination of labor as surely as a bony obstruction. We see this muscular obstruction for the most part in the excitable nervous patient or, as we like to term her, "the patient who just won't let go." Deep anesthesia is not good for the parturient woman. Very often she has had a long labor with its debilitating effects. If there is more than the usual bleeding deep anesthesia aggravates and exaggerates the shock syndrome. Zweifach and Hershey have conclusively shown how any but the "lighter" anesthetics have a predisposing action to the shock syndrome from blood loss.⁹

The effect on the baby of deep anesthesia is well known. The mother has had analgesia before. That combined with the anesthetic is enough to make resuscitation difficult and too often causes anxious moments to the obstetrician and distress to the baby.

It was the problem of deep anesthesia that led us to the use of curare in our delivery room. To date, April 1, 1950, we have used curare for 100 deliveries, including low forceps 60, midforceps 33, spontaneous 4, and breech 3.

When the patient is ready for delivery, she is taken to the delivery room and cyclopropane anesthesia started. After she is draped and catheterized, an estimate is made of the firmness of the perineum and the levators. (Sometimes, because of very firm levators the anesthetist is told during the transportation of the patient that curare will be used.) Eighty units of curare are then given. If there is no relaxation in ninety seconds, 20 more units are given. We have found that usually 100 units of the drug is the optimum dosage. As soon as the injection of curare is begun the cyclopropane is discontinued and only oxygen is given. When the cyclopropane is discontinued, the bag on the machine is not emptied. Oxygen is continued throughout the delivery. Very often that is all that is necessary for even the finishing of the repair of the perineotomy.

Results have been good. No baby has shown any effects from the drug whatsoever. In fact, because of the discontinuance of the anesthetizing agent we have had more of them cry immediately upon delivery than before. Not often is actual anesthesia given for more than five minutes.

An estimate of the relaxation obtained has been made two minutes after the intravenous introduction of the drug. With two exceptions we found the relaxation remarkable, so much so that on numerous occasions it has been a cause for comment. Because of this relaxation most of the episiotomies were shallow, and the transversus perinei was not severed. All episiotomies were midline. In one episiotomy there was an infection in the upper angle, but not enough to require repair. This could in no way be attributed to the use of curare. A probable explanation for the cause of the poor relaxation in two cases could be the extensive scar tissue from previous lacerations.

No patient had to have Prostigmine to counteract the effects of curare. One, because of marked respiratory depression, was given forced oxygen.

At the postpartum examinations of these patients who have returned, the perineums have been found firm. No puerperal gynecological operations were done, so some of the multiparas presented the relaxation they had had before pregnancy.

We believe the addition of curare to the armamentarium of the anesthetist has been of great benefit. It should be emphasized, however, that it be used only by one familiar with its actions and that one should be cognizant of its dangerous aspects and be able to cope with them.

While this study was in progress we heard of the work of Katzman and others.¹⁰ Their conclusions are the same as ours.

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944 MAIN STREET

Department of Case Reports

New Instruments, Etc.

CERVICAL EPITHELIAL CHANGES OVER A THIRTEEN-YEAR PERIOD TERMINATING IN EPIDERMOID CARCINOMA

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IN THE recent literature dealing with epidermoid carcinoma of the cervix, much attention has been focused on certain atypical changes in intact squamous epithelium which resemble those changes seen in invasive squamous-cell carcinoma. Similar changes in the skin have been referred to for many years as Bowen's Disease. In the cervix these changes have been given several synonymous names, among the most widely used being carcinoma in situ, preinvasive carcinoma, and intraepithelial carcinoma. The last, perhaps, is the most accurate descriptive term. In addition to these rather profound changes in the epithelium, certain atypical changes of a similar but less-marked degree, although long recognized, have been recently emphasized. These changes are localized in the basal portion of the epithelial layer, may extend for varying distances toward the surface, and have been termed by some "basal-cell hyperactivity." The possibility that these relatively minor changes may represent an early phase in the development of epidermoid carcinoma has stimulated much discussion and dissension.

This case report deals with a series of cervical biopsies taken from the same patient at irregular intervals over a thirteen-year period which seem to show a progression from a benign hyperactive epithelium to invasive carcinoma. An attempt was made to photograph characteristic areas in each of the biopsy sections, but presentation of such equivocal material with photomicrographs is understandably difficult.

When first examined in the gynecological outpatient department on June 8, 1937, the patient was 46 years of age, had had four pregnancies and four term deliveries. She complained of a profuse vaginal discharge. Examination revealed old deep bilateral cervical lacerations extending into the vaginal mucosa on the right, and erosion on both the anterior and posterior lips of the cervix. The cervix was cauterized with the actual cautery. Approximately seven weeks later examination revealed that the cervix was not healing and bled easily on manipulation. The first biopsy was taken at this time (Fig. 1).

Following this first biopsy the patient continued to have a blood-tinged discharge, the cervix still showed erosion and bled easily on contact, and Trichomonads were found on one occasion in the vaginal secretions. By April, 1938, the cervix had been cauterized three times with the actual cautery and twice with silver nitrate without resultant healing, and on April 13, 1938, the patient was hospitalized and electrocoagulation of the cervix, dilatation and curettage, and perineorrhaphy done. No pathological studies on the removed cervical tissue are available. During the next 11 months the cervix again failed to heal properly, being cauterized once with silver nitrate and once with the actual cautery. On March 15, 1939, a small suspicious lesion was noted on the posterior lip of the cervix, and this was biopsied (Fig. 2). A rebiopsy was requested because of the suspicious nature of the sections, and this was carried out on May 1, 1939 (Fig. 3). Although reported as benign epithelial hyperplasia with infection, another biopsy was requested, and this was carried out two weeks later (Fig. 4), showing essentially the same picture.

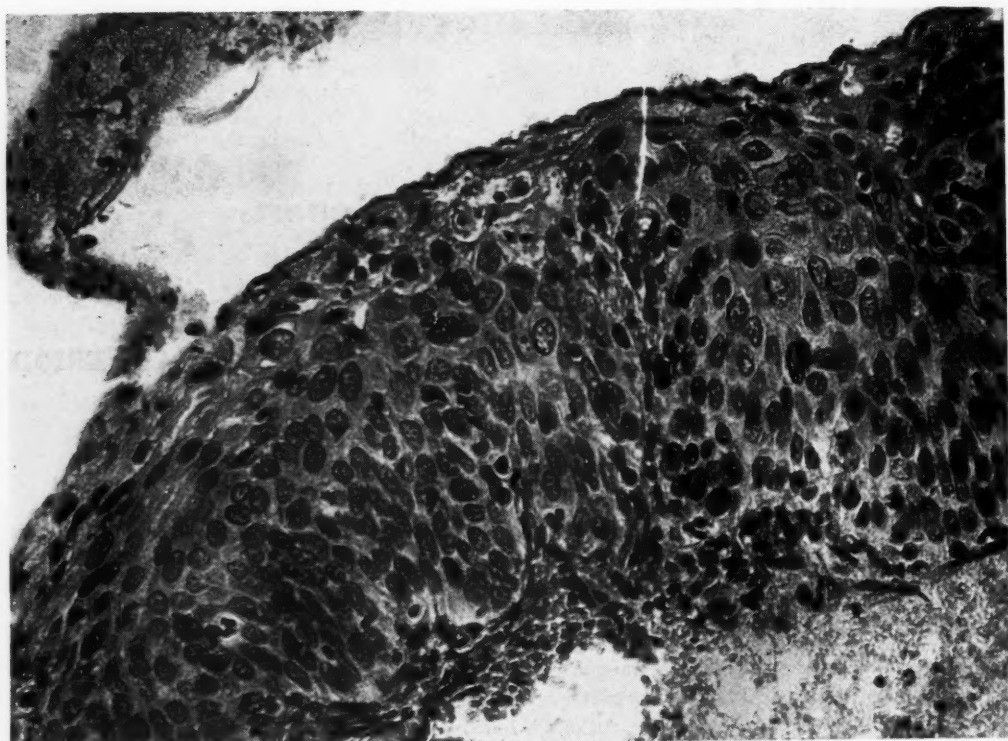


Fig. 1.—Biopsy of cervix, July 27, 1937.

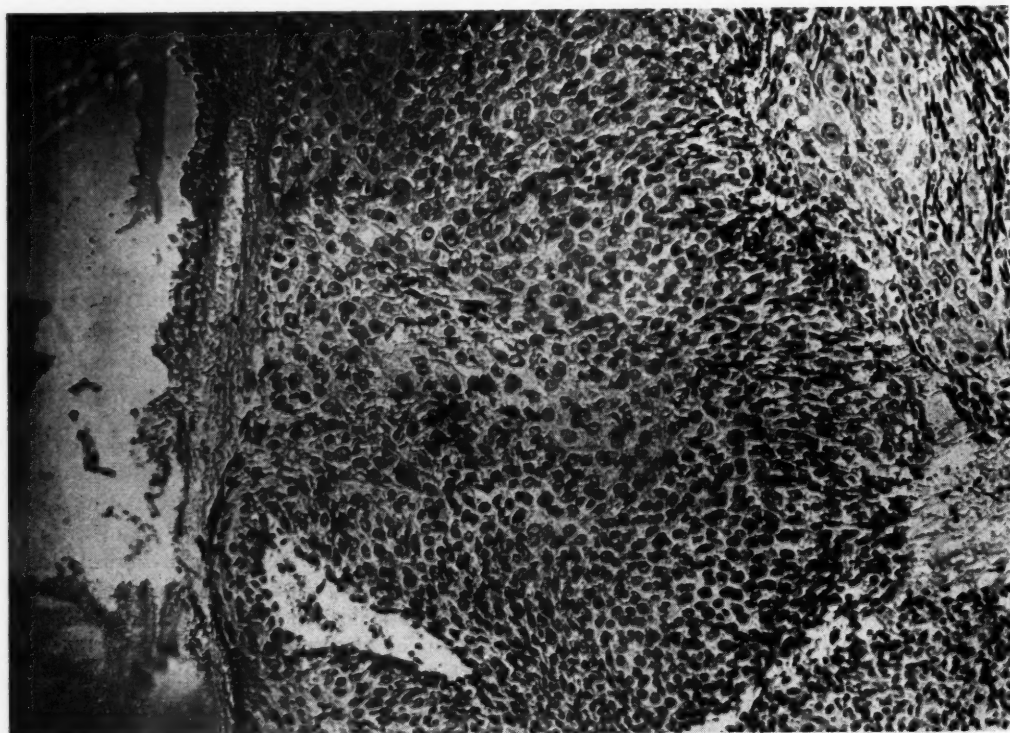


Fig. 2.—Biopsy of cervix, March 15, 1939.

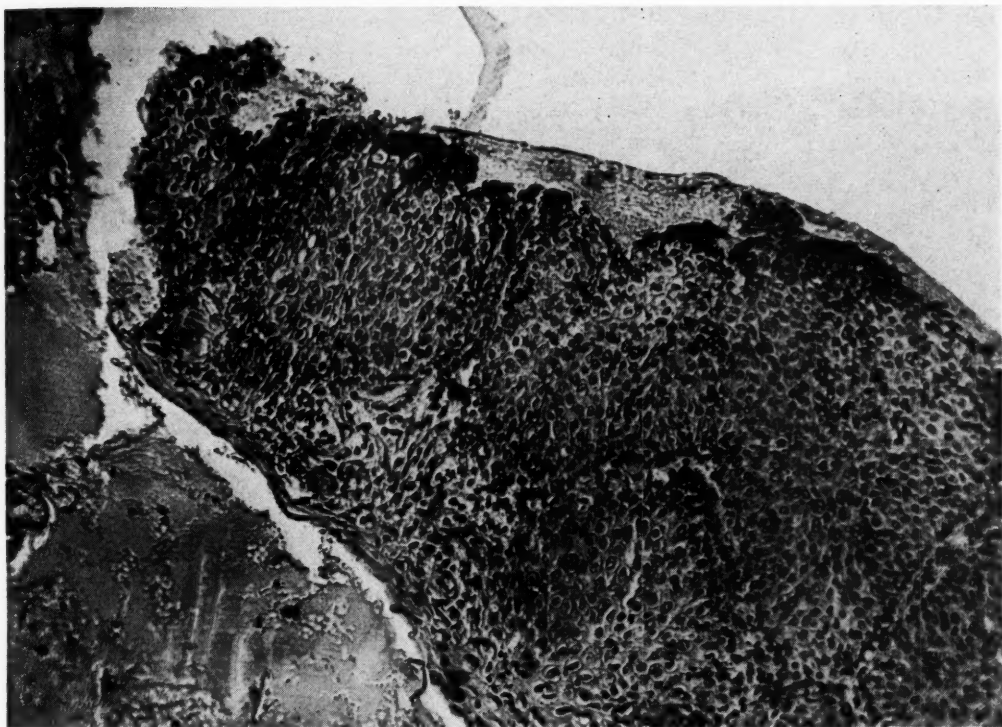


Fig. 3.—Biopsy of cervix, May 1, 1939.

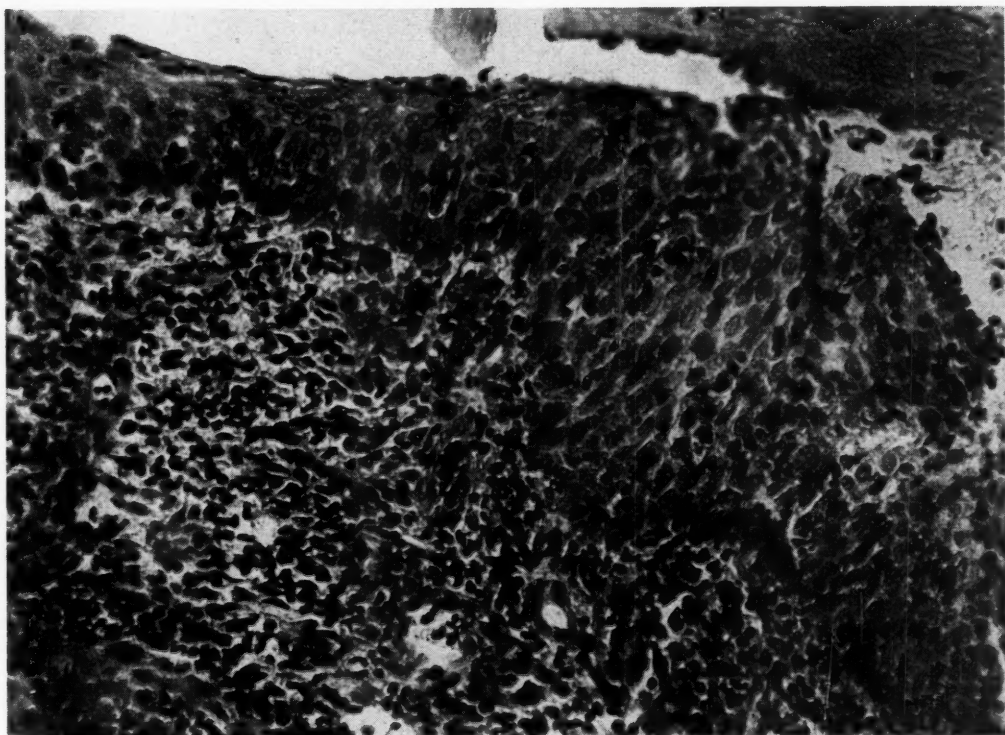


Fig. 4.—Biopsy of cervix, May 15, 1939.

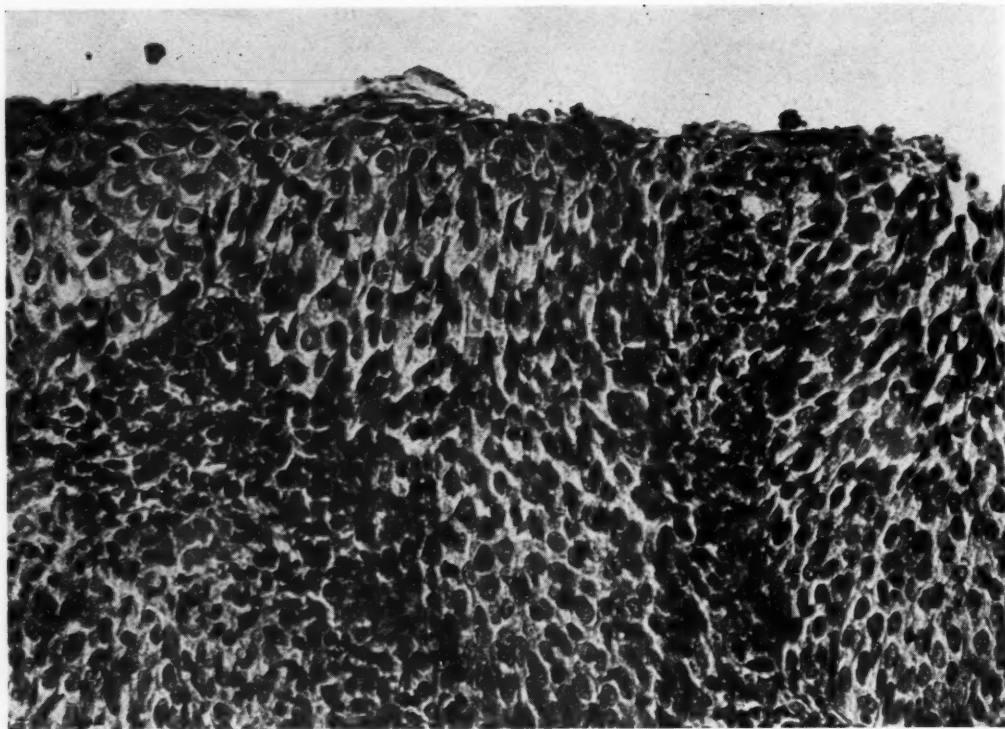


Fig. 5.—Biopsy of cervix, Jan. 24, 1950.

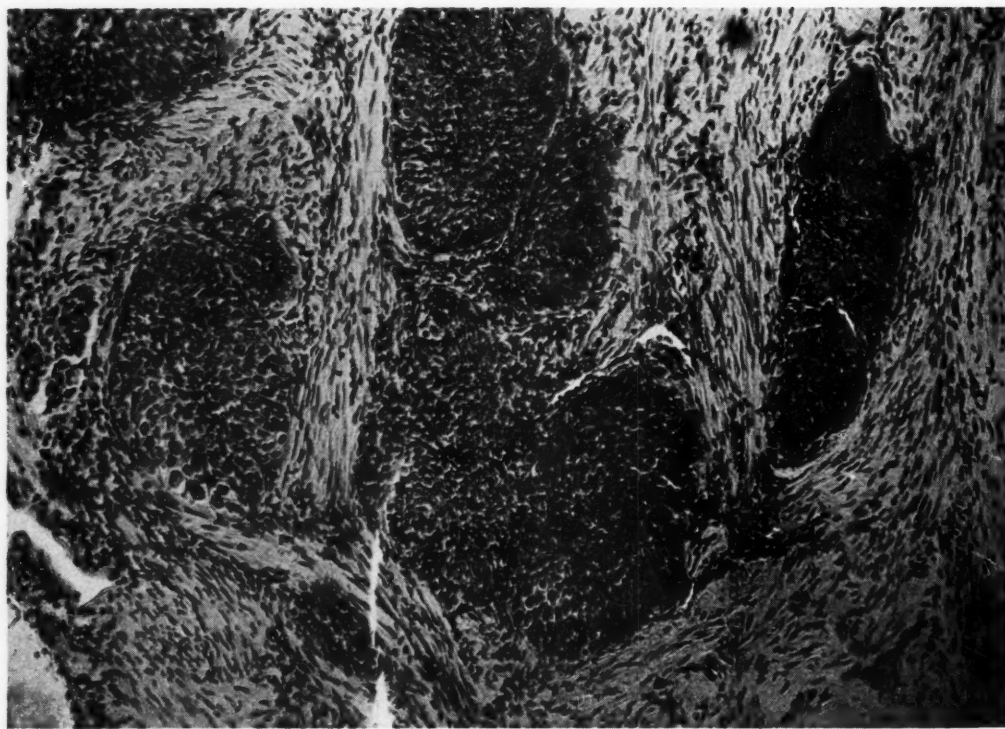


Fig. 6.—Surgical conization of cervix, Feb. 8, 1950.

For six months following this, the cervix still showed some erosion and was treated with silver nitrate and the actual cautery. Although senile changes were becoming apparent at this time, the erosion then appeared to heal, and only nodularity persisted. Some stenosis of the external os was noted in July, 1941, and bleeding occurred after probing and sounding the os. A foul discharge persisted and *Trichomonads* were found to be present. In November, 1942, the cervix was described as almost healed, and the patient was not seen again until July, 1948. The examination in the surgical outpatient department at this time showed senile vaginitis but no remarkable lesions of the cervix. In May, 1949, a gynecological examination was done because of a history of bloody vaginal discharge for two weeks. Senile vaginal changes were present, but no lesions were noted on the cervix at that time. Vaginal bleeding occurred on only one occasion after this, but on Jan. 24, 1950, at which time the patient was 58 years of age, a small, friable area was noted on the posterior lip of the cervix, and this was biopsied (Fig. 5). This was interpreted as intraepithelial carcinoma, but invasion could not be excluded because of the small amount of stroma included in the biopsy. Two weeks later the patient was hospitalized and diagnostic surgical conization of the cervix carried out (Fig. 6). This was interpreted as representing invasive epidermoid carcinoma.

Summary

A series of biopsy sections taken from the cervix of a patient over a period of approximately twelve years and seven months, from age 46 through 58 years, has been presented.

Careful re-evaluation of these sections has shown what appears to be a change from a benign hyperactive epithelium to invasive epidermoid carcinoma. Marked chronic inflammation was noted in all the tissue, and did not respond to vigorous treatment.

The material presented suggests only that invasive epidermoid carcinoma of the cervix may be preceded for several years by recognizable atypical epithelial changes.

PRIMARY ADENOACANTHOMA OF THE OVARY

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THE tumor known as adenoacanthoma or adenocarcinoid was first described by Herxheimer in 1907.¹ The term is applied to tumors of a glandular origin in which a metaplasia of the epithelium to a squamous type² occurs to a varying extent, but with obvious preservation of the glandular nature of the lesion. Such tumors are not uncommon in the uterus, forming about 3 per cent of endometrial carcinomas,³ and have been described in many other sites such as esophagus, stomach, pancreas, lung, gall bladder, colon, and breast.

Adenoacanthoma occurring in the ovary is rare and few cases are recorded in the literature. Meigs⁴ describes two cases of adenoacanthoma of the endometrium with ovarian metastases. Simpson and Branch⁵ report a questionable adenoacanthoma of the ovary which was, however, interpreted by several competent observers as a Brenner tumor from which they must be distinguished. In a review of the literature available to us the two cases reported by Melody, Faulkner, and Stone⁶ are acceptable as primary ovarian adenoacanthomas. Both of these occurred in cystadenocarcinomas of the ovary. Kuzma⁷ reported two cases associated with endometriosis. Of these, one was a cystadenoma with metaplasia (adenoacanthoma) and a small endometrial focus of adenoacanthoma interpreted by the author as either metastatic from the ovary or coincidental. The other, from the author's description would appear to have developed in a focus of endometriosis and is undoubtedly a primary ovarian lesion.

Case Report

No. 44,224. A 53-year-old white woman was admitted to the Woman's Division of the Pennsylvania Hospital, on the service of Dr. J. Vernon Ellson, complaining of a mass in the lower abdomen. This had first been noticed four months previously during an episode of lower abdominal pain. There was no recurrence of the pain, nor were there other subjective symptoms. The menses had begun at 12 years with a 5-day flow every 28 days. She had had one normal pregnancy and no abortions or miscarriages.

Five years previous to admission she had been seen elsewhere because of menorrhagia. At that time pelvic examination revealed a small cervical polyp, endocervicitis, and a symmetrically enlarged uterus. The adnexa were negative to palpation. A diagnostic curettage and cervical biopsy were reported as endometrial hyperplasia and chronic cervicitis. After endothermic resection of the cervix, an intrauterine application of radium was employed for a total dosage of 1,800 mg. hr. Following this there was complete cessation of the menses and there had been no postmenopausal vaginal bleeding.

Further past medical history revealed diphtheria in childhood, thyroidectomy for removal of a toxic adenoma 15 years previously, and diabetes mellitus, which was well controlled with diet and small amounts of insulin.

Physical examination revealed a mild hypertension (150/100) but no other significant findings apart from the lower abdominal mass. This was present as a nontender, firm, irregular, midline, lower abdominal mass, which appeared to arise in the pelvis and extend almost to the umbilicus. On pelvic examination the vaginal outlet was well supported and the cervix was clean. The entire pelvis was filled by a firm irregular mass and neither the corpus uteri nor the adnexa could be specifically identified.

A laparotomy was performed under spinal and Pentothal Sodium anesthesia. The right ovary was cystic and nodular, and measured approximately 18 cm. in its greatest diameter. The ovarian cyst was adherent to the broad ligament anteriorly and to the large bowel posteriorly, with its corresponding Fallopian tube being drawn over its superior surface. The corpus uteri was atrophic, and the left ovary and Fallopian tube appeared normal. Supravaginal hysterectomy, bilateral salpingo-oophorectomy, and appendectomy were per-

formed. While the ovarian cyst was being dissected free from its attachments, the cyst wall was torn with ensuing spillage of a portion of its contents into the peritoneal cavity. The postoperative convalescence was uneventful, and the patient was discharged from the hospital on the eleventh day following operation.

Pathologic Examination (S.48-1201).—

Gross: The specimen consisted of a supracervically amputated uterus, both tubes, and both ovaries. The uterus measured 3.5 by 5 by 3 cm., and its serosal surface was smooth, shiny, and pink. The uterine cavity was patent and contained a small amount of dark fluid. Its lining was smooth, shiny, and pale gray pink. The myometrium was pinkish white, firm, pliable, and 1.8 cm. in thickness.

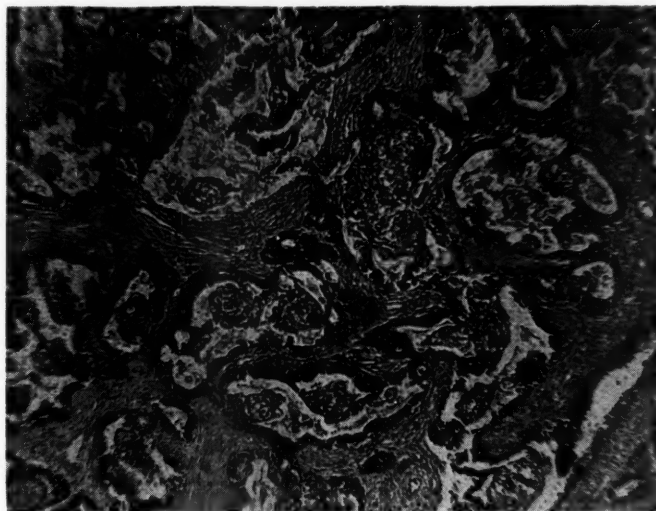


Fig. 1.—Section through inner margin of cyst wall showing glandular pattern with central squamous-cell masses. (Zenker H. & E. $\times 100$.)

One tube was 7 cm. by 0.4 cm. The serosa was smooth, shining, and pink. The lumen was patent and the mucosa was shiny, and thrown into folds. The corresponding ovary measured 3 by 1.2 by 0.4 cm., and the surface was pinkish yellow, shiny, and slightly irregular. The cut surface was homogeneous and white. The other tube was 15 cm. in length and 0.4 cm. in diameter. The mucosa was smooth, shining, and thrown into folds. The corresponding ovary was cystic and had been previously opened. It measured 12 by 10.5 by 5 cm. The external surface was shiny and irregular and varied from greenish gray to bright pink. On section the cyst was multilocular, having a few large locules. For the most part, the lining was shiny and bright pink. Projecting from the inner walls in a flattened manner were small, grayish tan to yellow elevations which were firm and in some instances had a gritty consistency. The wall of the cyst measured 0.2 cm. in thickness. The appendix was grossly normal in appearance.

Microscopic: The uterus revealed an atrophic myometrium with small muscle bundles and a marked hyalinization of the vessels and perivascular fibrosis. The endometrium was composed of cystically dilated glands containing a basophilic mucoid material and lined by flattened cuboidal amphophilic cells with small central vesicular nuclei. The stroma was relatively acellular, the stromal cells being replaced in large part by acidophilic collagen. The picture was typical of a retrogressed endometrial hyperplasia. There were no significant changes in the tubes. There was marked arterial hyalinization and numerous corpora albicantia were present in the smaller ovary. Primordial follicles or their cystic derivatives were absent. There were numerous small cysts lined by a single layer of cuboidal to columnar amphophilic cells with central round vesicular nuclei. These were typical germinal inclusion cysts.

Sections of the large ovarian cyst revealed a dense wall of acidophilic collagen. There was no residual normal ovarian tissue. The lining was composed of cuboidal to low columnar cells with large round to oval central vesicular nuclei. At many points this epithelium was heaped into papillary folds. Some of the coarser papillary projections had a dense fibrous stroma. In addition, the epithelium grew into the wall of the cyst in a glandular pattern which was also reproduced in the papillary folds. The epithelial lining of the intramural cystic structures often followed a papillary course. At many points through the deeper glandular structures as well as along the free margin there was a focal transformation of the central cells to a squamous type, the individual forms being large polyhedral and acidophilic (Fig. 1). Some of these contained densely acidophilic masses of keratohyalin (Fig. 2). There were also so-called epithelial pearls with a central mass of keratohyalin surrounded by concentrically arranged squamous cells, the latter blending peripherally with columnar glandular cells, and in every instance the peripheral segment of the focus was of a glandular pattern. In no instance did the squamous-cell element occur alone or invade the stroma as such. The histological picture of this lesion was that of a serous cystadenoma, which had undergone malignant change, giving rise to an adenocarcinoma with squamous metaplasia producing a lesion typical of the so-called adenoacanthomas.

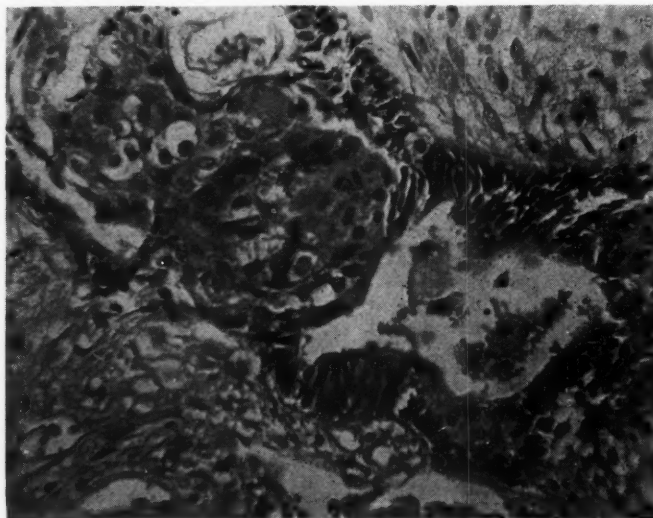


Fig. 2.—Detail of single gland showing columnar lining and central nest of polyhedral squamous cells with a ball of keratohyalin at upper edge of nest. (Zenker H. & E. $\times 500$.)

No significant changes were noted in the appendix.

Pathological Diagnoses: Uterus and Fallopian tubes, retrogressed hyperplasia of the endometrium. Germinal inclusion cysts, senile atrophy of one ovary. Adenoacanthoma arising in a serous cystadenoma of the other ovary. Normal appendix.

The patient was apparently well until nine months following operation, at which time she developed an upper respiratory infection. This was accompanied by a cough which was productive of a mucoid sputum. Hemoptysis was never present. Shortly thereafter a firm nodule was noticed in her neck. Roentgen-ray therapy to the neck and chest was given elsewhere. The exact nature of the therapy is not known. During the course of roentgen-ray therapy nausea and vomiting developed, and there was a loss of twenty pounds in body weight.

One year after operation the patient was re-admitted to the hospital complaining of back pain in the upper lumbar region of three weeks' duration. The pain was intensified with exercise and was becoming progressively more severe.

Physical examination at this time revealed a hard, nontender, mobile mass, the size of a small egg, over the right sternoclavicular joint. Further firm nodules could also be palpated in the right axilla and in both groins. Scattered throughout the subcutaneous tissue over the abdomen and buttocks were multiple nodules varying from pea to golf-ball size. No other pertinent physical findings were demonstrable.

Roentgen-ray examination of the vertebral column showed evidence of questionable metastatic lesions in the bodies of the tenth and eleventh thoracic vertebral bodies. Biopsy of a lymph node in the left groin was then performed (S.49-2242).

Urethane was administered unsuccessfully for the relief of pain. The patient's general condition deteriorated rapidly, and death occurred thirteen months following pelvic surgery. Autopsy was not permitted.

Pathologic Examination of Lymph Node: (S.4912242).

Microscopic: There was replacement of the normal structures by islands of squamous cells showing frequent mitoses. Some cells contained keratohyalin, and there was an attempt at pearl formation. No glandular elements or attempts at gland formation were present.

Pathologic Diagnosis: Epidermoid carcinoma, Grade II, metastatic to lymph node.

Comment

The adenoacanthomas of the uterus behave as do the adenocarcinomas, which are well differentiated and usually slow growing (Grade I). Novaks states that squamous metaplasia is most often seen in the better differentiated endometrial tumors, and in our own experience this is true also of the adenoacanthomas occurring elsewhere. It may be reasonably presumed that the ovarian lesions behave similarly, and the malignancy of a given adenoacanthoma would be dependent upon invasion and pleomorphism of the glandular components rather than upon the metaplasia. The lesion, therefore, in regard to treatment and prognosis, may be considered as a cystadenoma or cystadenocarcinoma of corresponding differentiation.

The unfavorable outcome in this particular patient may well be related to the laceration of the ovarian lesion in the process of removal. It is probable that the tumor spread as an adenoacanthoma, but with ultimate complete replacement of the glandular by the squamous elements. This is the only adenoacanthoma of the ovary encountered in 104 serous cystadenomas at this hospital. While the lesion is uncommon, many more must have occurred than the few recorded in the literature would seem to indicate.

Neither our case nor other reported cases offer any contribution as to the histogenesis of the metaplasia. One theory is that the squamous cells develop from undifferentiated cells beneath the normal columnar epithelium. Second, it may represent a direct change in the character of the cells which one not infrequently sees in normal cells under the influence of infection in such sites as the cervix and bronchi. It is unlikely that Walthard's rests are of any significance in the genesis of ovarian adenoacanthomas, but one must carefully distinguish a Brenner tumor, showing transitions to a pseudomucinous cystadenoma, from an adenoacanthoma. In the former the abundant fibrous stroma is quite characteristic, and the epithelial cell groups (presumably derived from Walthard's rests) do not contain keratohyalin or show pearl formation.

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SPONTANEOUS PERFORATION OF THE BOWEL INTO GRAVID UTERUS NEAR TERM

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MRS. H. E., a 37-year-old para i, gravida ii, first child 12 years old, was first seen in the Obstetrical Clinic on Jan. 18, 1950. The only previous medical attention was two years ago when she went to a local doctor for undisclosed reasons and was told that she had "tumors" of the uterus and would not be able to become pregnant. She declined surgery at that time. Her first pregnancy had been uneventful. The last normal menstrual period was April 6, 1949. Pregnancy was uneventful until two weeks before the date she was seen, when she started having mild vaginal bleeding. At about the same time she ceased to feel fetal movements. In the interval before coming to the clinic she had anorexia and vague discomfort in the region of the pregnant uterus.

Examination when she was first seen showed an ambulant, not acutely ill woman with the abdomen suggesting pregnancy near term. The abdominal mass was quite firm, smooth, and symmetrical. Because of its firm consistency and because no fetal parts or fetal heart tones were found, an x-ray was ordered. The x-ray was not clear enough to allow a decision as to whether or not the fetus was alive, but showed a near-term fetus in left sacrotransverse position.

The patient was told to return in one week if labor did not supervene.

The patient was next seen on Jan. 21, 1950, when she came to the emergency room complaining of chills and fever and with vaginal spotting. Temperature was 103.4° F. The abdomen was as before with no fetal heart tones but somewhat softer so that fetal position could be verified clinically as left sacrotransverse. Red blood count was 2.9 million, hemoglobin was 5.2 Gm. One thousand c.c. of whole blood were ordered but the patient could not be cross-matched until Jan. 23, 1950. She was started on Hypercillin 1 c.c. twice a day and fluids were forced orally.

The temperature continued to be of the septic type, reaching a peak of 103° to 104° daily. Repeat x-rays, clearer than before, showed roentgen evidence of fetal death. Examination and attempt to rupture the membranes were made. The cervix was found to be firm and of the nonpregnant size. The cervix was turned upward toward the symphysis and displaced anteriorly. The external os easily admitted the finger but the cervical canal quickly coned down to an apparently blind end. Uterine dressing forceps could not be passed beyond the internal os by gentle probing and later by quite vigorous pressure. The parametrium and cul-de-sac areas were indurated and firm, forming an ill-defined wall across the pelvis. This induration was firm and semiplastic but not particularly tender. These pelvic findings were confirmed by different examiners on the subsequent two days and two additional attempts at rupture of the membranes were unsuccessful.

On January 24, the patient was started on streptomycin, 0.5 Gm. four times a day, and was given a second transfusion of 500 c.c. blood. It was decided that abdominal hysterotomy would be done on January 27, with the intervening time allowed for an attempt to combat the infection with the antibiotics.

On January 26, the patient's abdomen was softer than before and crepitus of the fetal skull was easily appreciated.

On January 27, under spinal and later cyclopropane anesthesia, the abdomen was opened through a left suprapubic paramedian incision. The uterus was firmly adherent to the anterior

abdominal wall. The parietal and visceral peritoneum were, together, thickened to approximately $\frac{1}{4}$ inch. The anterior surface of the uterus was exposed by blunt dissection for an area large enough to give working space, then the uterus was entered through a vertical incision.

The uterine wall was thin, pale, and did not bleed when cut. The amniotic cavity contained a small amount of thick, green, putrid-smelling material. The fetus was badly macerated and the placenta was necrotic so that it was scraped from the uterine wall in handfuls. The uterine wall itself was grayish white, thin, and possessed of no contractility at all, collapsing like a balloon when the products of conception were removed. There was no bleeding from the placental site or the uterine incision. Dissection of the collapsed uterine walls from the densely adherent omentum, small bowel, and large bowel was started in an effort to remove the uterus. On the upper part of the posterior aspect of the fundus such dense adhesions were found between sigmoid and fundus that after entering the bowel once and repairing it, further dissection was abandoned in this area. Bilateral dissection to encircle the fundus and reach the cervix was tried and succeeded. A fibroid tumor 4 cm. in diameter was found in the anterior wall of the uterus near the endocervix and overlying the internal cervical os. A supracervical amputation of the fundus was done to include the fibroid. The cervical cuff, which was closed with continuous lock sutures of No. 0 chromic catgut, was the only part of the uterus which showed enough vascularity to bleed when cut. Further removal of the fundus by dissection upward was successful to within 4 to 4.5 cm. of the point reached previously from above. At this lower point an opening from the sigmoid to the cavity of the uterus was found with smooth, rounded edges, suggesting that it had been present for some time. The neighboring adherent uterus was dissected from the bowel wall and the bowel was repaired with No. 000 atraumatic suture. Further attempts to remove the remaining uterine wall, which measured about 6 by 8 cm. was not attempted. Colostomy was not done because of the gross infection in the lower abdomen and for fear of conveying the infection to the upper abdomen which had been avoided up to this point and because it was felt that the repairs of the bowel would be adequate provided no further bowel-wall necrosis took place, in which case a colostomy would be to no avail.

The remaining uterine wall was placed over the area of the vaginal cuff and the space between the two was drained with a Penrose drain through a right-lower-quadrant stab wound. The incision was closed with No. 0 chromic catgut doubled for peritoneum and fascia and clips for the skin.

The patient reacted from anesthesia within an hour and sustained no greater drop in blood pressure than to 95/70. Five hundred c.c. of whole blood were given in the operating room and 500 c.c. more were given when the patient reached her room.

The high points of the postoperative course were as follows:

Postoperatively the patient did better than expected for some time. She was given penicillin and streptomycin, fluid balance was maintained by intravenous fluids and, despite the fact that the patient felt hungry, a Miller-Abbott tube was put down on the third day when she started to develop moderate distention. The temperature, which subsided somewhat for the first forty-eight hours, went back to the 101-104° F. area and stayed there after the third day. Fecal drainage from the stab wound was first noted on the third day. The patient also passed feces by rectum from the third day on.

On the seventh postoperative day at 4:30 A.M. the patient ceased to breathe, became cyanotic, and lost consciousness. She was revived by stimulants to irregular, gasping respirations, and was put on nasal oxygen. Within an hour of the onset of this change she became very restless and was given sedation to keep her quiet. By 1:00 P.M. she became lucid again and oxygen was discontinued. There were no apparent aftereffects from this episode. The patient was given heparin for four days following.

During the following days the patient seemed to improve slowly. The Miller-Abbott tube was removed on the eleventh day and the patient was carried on a high-protein liquid diet, oral antibiotics, and nonabsorbable sulfonamides, plus oral vitamins. The abdominal

wound broke down to the rectus muscle and was reapproximated after being cleaned up. The cervical cuff opened and established a fistula. By the twenty-second day, despite these changes, the patient was improving clinically and was allowed to sit up for a period twice daily.

From the twenty-second to the twenty-eighth day, the temperature fell from an average of 103 to an average of 99.6° F.

On the twenty-sixth day, she had a small hemorrhage of about 100 c.c. from the vagina and abdominal drain.

On the twenty-eighth day, she had a severe hemorrhage from the same sites and was given 500 c.c. whole blood. She seemed to recover well after the transfusion.

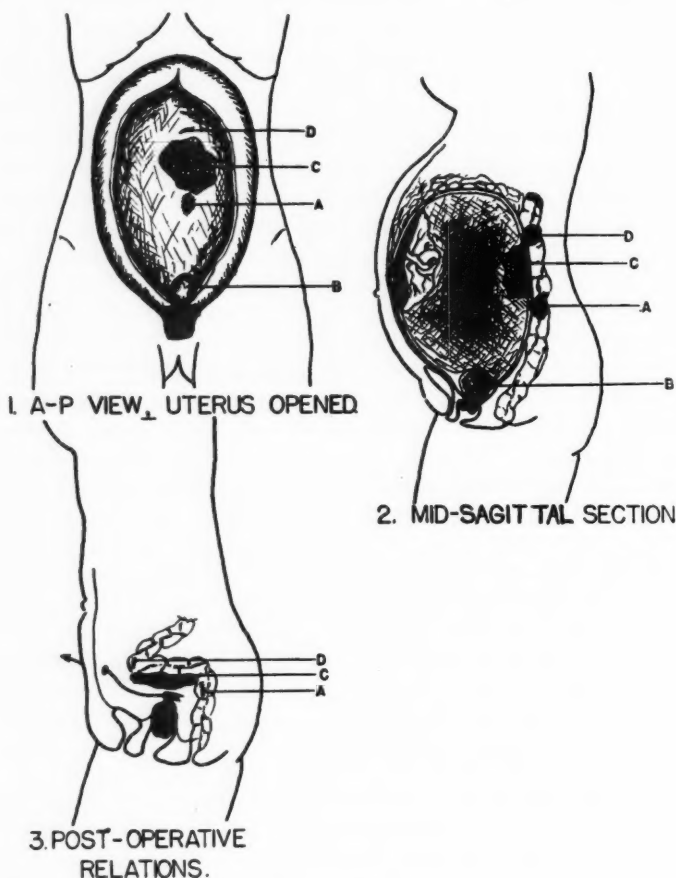


Fig. 1.—Anteroposterior view, uterus opened.

- A. Original perforation.
- B. Fibroid.
- C. Portion of wall left in.
- D. Site of Operative Perforation.
- Uterine tissue not removed.

On the twenty-ninth day, the patient was listless, refused food, skin turgor was poor, and her temperature had dropped to subnormal levels. Continuous intravenous fluids were started through a cut-down in the leg. Protein hydrolysate and 5 per cent glucose in normal saline, each 1,000 c.c., were planned daily, the cannula to be kept open with 5 per cent glucose in water at other times. Five c.c. Betalin compound were added to each liter of saline.

On the thirtieth day, at 9:35 A.M., and with no further incident, the patient's pulse became imperceptible and she ceased to breathe.

Pertinent parts of the autopsy report are as follows:

When the lower abdomen was opened, a large cavity was entered, measuring about 10 by 12 cm. by 8 cm. The cavity was filled with black liquid fecal material and old blood clots. The cavity was entered by the stab wound to the outside and by the open cervical cuff into the vagina. The rectum lay behind the cavity, the abdominal wall in front of it, the intact bladder and open cervical cuff below, the pelvic walls lateral, and conglutinated large bowel and small bowel above.

There was an opening in the colon at the rectosigmoid junction measuring 1 by 2 cm. into the cavity. About 8 cm. above this point the colon wall was eroded away for approximately 4 cm., leaving only a strip of colon wall about 2 cm. wide. There were two extensions of this cavity. One measured about 1½ cm. in diameter, extended retroperitoneally up the left gutter for 7 cm., and ended. The second extended 4 cm. into the matted intestines forming the upper wall of the cavity. The intestines above the roof of the cavity were relatively free of adhesions except at two points where loops of jejunum were found adherent over small fecal abscesses, both containing about 5 to 10 c.c. of yellow purulent matter. The abscesses were separate from the large cavity described above and had arisen in the lymphatics of the mesentery of the intestine.

Cause of Death.—Septicemia.

Contributory Causes of Death.—1. Fecal fistula with gangrene and peritonitis. 2. Massive hemorrhage in pelvic cavity.

Comment

The literature reveals this to be a very rare condition, including 58 entero-uterine and 13 sigmoido-uterine fistulas. However, these were the result of infections, labor with impaction of the fetal head, or instrumentation. In this case, none of the above situations prevailed. It seems logical that it should originate from the uterine side. In keeping with this it was noted at operation that there was a slight relative thickening of the uterine wall in the area of the perforation. This could have been a myoma which carried a degenerative process through the intestinal wall. This thickened area was a part of the uterine wall left attached to the sigmoid. At autopsy this had sloughed away so that no tissue section could verify the supposition.

The thin, parchment-like, bloodless aspect of the entire uterus is likewise interesting. It gives rise to the conjecture as to whether the tumor in the pelvis had chronically impaired its blood supply, this in turn causing degeneration.

In retrospect it would appear that a colostomy should have been done. However, odd as it may look in print, the intestines were such a tortuous, adherent mass that it was difficult to distinguish one part from another. In addition to the other reasons given above, the anesthetist stated that the patient was in critical condition and asked that the operation be terminated as rapidly as possible.

PRIMARY CARCINOMA OF THE VAGINA ASSOCIATED WITH PREGNANCY

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PRIMARY carcinoma of the vagina is relatively rare. This lesion makes up less than 1 per cent of all carcinomas in the female.¹ It represents 1.09 per cent (Emmert²) to 2.7 per cent (Taussig³) of the malignancies in the female genital tract. The average age of patients with primary carcinoma of the vagina has been variously stated, but it occurs most commonly in the sixth decade of life.^{1, 4, 5}

Considering the age incidence of primary carcinoma of the vagina, one would expect the association with pregnancy to be extremely uncommon. So far as we have been able to determine, there has been only one other case reported in the American literature in the past twenty years. This case, reported by Tuft,⁵ was treated with radium following cesarean section, and the mother died three months later, having already developed a rectovaginal fistula.

In view of the rarity of primary carcinoma of the vagina associated with pregnancy, the following case is reported.

L. P. (199,604), a Negro married woman, 23 years of age, para 0, gravida i (present pregnancy), was first seen with the present illness on Jan. 13, 1948. She was admitted to the hospital on this date with the chief complaint of cramping around the umbilicus. She had had no menses since Oct. 28, 1947 (expected date of confinement Aug. 4, 1948). History revealed spotting on Nov. 29, 1947, occasional nausea and vomiting and frequency of urination since last normal menstrual period. Onset of menarche was at the age of 15 years, and menstruation had previously been regular every 28 days with duration of flow 4 to 5 days. Past history revealed meningitis at 6 years of age, with no sequelae. The patient had been followed irregularly in the Outpatient Clinic for the past six months for obesity and hypertension.

Admission examination revealed weight to be 201 pounds, height 5 feet, 2 inches, and blood pressure 140/90. Pelvic examination showed the following findings: marital outlet with smooth, soft, closed, discolored cervix with a small amount of blood in the os; a hard lesion present in the posterior fornix, about the size of a pecan, which was thought to be granulomatous and which bled following manipulation; uterine fundus enlarged to size of three to four months' pregnancy. Results of laboratory tests were within normal limits, including negative Kahn test, and the Rh factor was positive. The patient became asymptomatic on bed rest and sedation. Repeat examination on the sixth hospital day confirmed the presence of a granulomatous lesion in the posterior fornix and biopsy was to be done in the Outpatient Clinic. She was discharged with the diagnosis of threatened early abortion.

The patient was then followed at regular intervals in the clinic. Through an oversight we failed to obtain her hospital record and biopsy of the lesion was not done. She had a pelvic examination on March 8, 1948, and some blood was thought to be oozing from the cervix, but no lesion was noted in the posterior fornix. She continued to complain of spotting and was treated with sedation, rest, stilbestrol, progesterone, and iron. She was placed on a diet because of obesity and hypertension. Blood pressure showed a satisfactory response from 190/106 to an essentially normal reading. The uterus continued to enlarge and the fetus was active.

On May 27, 1948, she was readmitted to the hospital because of uterine contractions and history of bleeding for three days. Hemoglobin was 8.5 Gm. on admission, but no bleeding was noted on inspection. She was not believed to be in labor. She was given a transfusion of whole blood. The next day she was thought to be in labor, and labor seemed to be progressive. She was placed on penicillin because of foul vaginal discharge. On May 29, 1948, after the cervix was thought to be completely dilated and no progress was made, a vaginal examination was done. The cervix was not dilated. It was smooth and showed no ulceration or evidence of tumor. The membranes were intact and the vertex was floating. An orange-sized mass, with a deep ulcer in the center bounded by hard margins, was found in the posterior fornix of the vagina. The lesion was friable and bled easily. It seemed to be more extensive on the left, but crossed the midline. A biopsy was obtained. Rectal examination confirmed that the mass was located in the rectovaginal septum. The rectal mucosa seemed to be intact. Fetal heart tones were good following the examination.

Frozen section examination of the biopsy specimen was reported as follows: "A papillomatous growth is seen containing many mitoses, some of which appear under frozen-section stain to be multipolar mitoses and occasional bizarre giant cells are seen."

The clinical impression was that of carcinoma of the vagina. The patient was given blood transfusions, and a low classical cesarean section was done. At operation, both kidneys were found enlarged, irregular, and with multiple cystic masses present. A small, marble-sized, firm subserous nodule was noted on the posterior surface of the fundus of the uterus. The mass in the posterior fornix was felt in the cul-de-sac, and noted to extend into the left broad ligament. Several nodes were palpable in the left iliac fossa. The liver was smooth and normal sized and lymph nodes along the abdominal aorta were not enlarged. The tubes and ovaries were normal. The findings were thought to be consistent with the diagnosis of advanced primary carcinoma of the vagina, possibly polycystic kidneys, and a subserous uterine fibroid.

The final pathological report revealed that the sections taken from the biopsy of the tumor mass were composed almost entirely of tumor which was made up of branching columns of anaplastic squamous epithelial cells. Keratohyaline production was noted, and numerous amitotic giant forms of tumor cells described. Tumor cells were seen within the lymph vessels. Diagnosis was squamous-cell carcinoma, Grade 3 to 4.

Postoperative course of the patient was morbid and she continued to run low-grade fever, although penicillin was continued and sulfadiazine started immediately after operation, together with intravenous fluids and blood transfusions. The abdominal wound healed primarily.

The baby was a female, delivered alive, and weighed 3 pounds, 4 ounces. She cried spontaneously but there was retraction of the thoracic cage on inspiration, and she expired thirty-nine hours after birth. The post-mortem examination of the infant revealed prematurity and atelectasis.

Pelvic examination on June 15, 1948 (seventeenth postoperative day), revealed the cervix to be smooth, firm, and displaced up behind the symphysis. The mass in the vagina had doubled its size since the previous examination. The fundus of the uterus was of normal size for this stage of involution. X-ray of chest, pelvis, and lumbar spine showed no evidence of metastasis. Intravenous pyelogram was suggestive of bilateral hydronephrosis.

The consulting radiologist advised deep x-ray therapy only. Because of the extent of the disease he felt radium would only hasten complications. She was given 2,400 r to each of six pelvic ports 10 by 15 cm. with a total dosage of 14,400 r. This was administered in thirty-five days.

Pelvic examination, following the completion of radiation, revealed the cervix not to be involved, although the vaginal mass was still present but had decreased in size. The fundus of the uterus was slightly larger than normal and was now fixed.

The patient ran a progressively downhill course in spite of another course of deep x-ray therapy three months later (total dosage of second series was 7,200 r). This was administered over a period of fifty-four days. She developed marked anemia and pyelitis.

She continued to have vaginal bleeding, and, following a hemorrhage at home, she was readmitted to the hospital for blood transfusions. On Feb. 23, 1949, she developed generalized convulsive seizures. At this time she was also noted to have developed a rectovaginal fistula. She continued to have convulsions and died on March 6, 1949, ten months after cesarean section and sixteen months following first pelvic symptoms.

An autopsy could not be obtained on this patient. We believe that this is a primary carcinoma of the vagina because of the original location of the tumor in the posterior vaginal vault. Clinically, there was never evidence of tumor in the cervix itself and microscopically the tumor was of a very anaplastic squamous-cell type.

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THREE GENITAL CANCERS IN ONE INDIVIDUAL

COURTLANDT D. BERRY, M.D., ORLANDO, FLA.

(From the Orange Memorial Hospital)

MRS. R. S., a 68-year-old white widow who had never been pregnant, was first seen on Feb. 23, 1949, complaining of leakage of urine, frequency and urgency. She gave a history of good health prior to 1940; however, in October of 1941, she was treated at the Roswell Park Memorial Institute, Buffalo, N. Y., for an epithelioma of the cervix (League of Nations, Grade III, Stage not recorded). Treatment at that time consisted of radium pack and intracavitary radium tubes in the uterus and against the cervix for a total of 9,500 r as a tumor dose. She was seen at frequent intervals at that hospital, with apparent freedom from disease as late as September, 1948. She moved to St. Petersburg, Fla., this same month, and underwent a repair of a cystocele because of presumed leakage of urine.

At the time of her initial examination on Feb. 23, 1949, the patient was losing weight, complained of urgency, frequency, and stated that on several occasions she was unable to void. She had had no vaginal bleeding, no chills, fever, hematuria, or vaginal discharge, but complained of some lower abdominal discomfort. A mass arising in the pelvis, extending well up into the abdomen, was found. The cervix was clean, considerably scarred, and stenosed. The remainder of the pelvic examination showed no abnormality. The cervix was biopsied, and a large amount of bloody fluid was encountered when the cervix was dilated. Pathological report of the cervical biopsy tissue showed chronic cervicitis, no evidence of malignancy. The pelvic mass decreased somewhat in size but never disappeared, and the drainage from the uterine cavity continued. The patient was rehospitalized in June of 1949, and an attempt was made to determine, by cervical dilation and intrauterine exploration, the cause of the continued uterine drainage. A large amount of necrotic, microscopically unidentifiable material was obtained from the uterus; laparotomy was then carried out and the operative findings revealed the omentum to contain obvious metastatic malignancy with the small and large intestines similarly involved. The tumor apparently arose from the fundus of the uterus and was extending through its wall in the superior portion, and was intimately adherent to an adjacent loop of intestine. The left tube was normal; the right tube and ovary and the left ovary could not be identified. The body of the uterus and the contained tumor were approximately 15 cm. in diameter. The uterus was fairly smooth over the peritoneal surface, except at the fundus. No liver, stomach, and kidney metastases were felt. The main uterine mass was removed but no attempt was made to enter into the regions of the bladder or rectum. At the conclusion of the procedure, it was felt that the patient would very likely develop intestinal obstruction in the relatively near future due to the extensive metastasis.

Pathological report of the tissues removed at this time follows:

Specimen consisted of: (1) A uterus without cervix measuring 14 by 12 by 11 cm. The serosa was congested and showed some broken fibrous adhesions. There was an irregular tear in the fundus through which projected a bulging tumor mass measuring 3 cm. in diameter. On section of the specimen there was found to be a large soft tumor growth approximately 11 cm. in diameter, forming the bulk of the specimen. Much of the tissue was degenerating with the formation of cystlike areas, hemorrhage, and necrosis. The gross appearance of the tumor had some of the characteristics of a fibroid tumor. However, the margins were not encapsulated though they were well circumscribed. The tissue in the margins appeared better preserved than that in the center of the tumor or that lining the uterine cavity. The shape of the uterine cavity was markedly distorted and pushed to one side by the large growth.

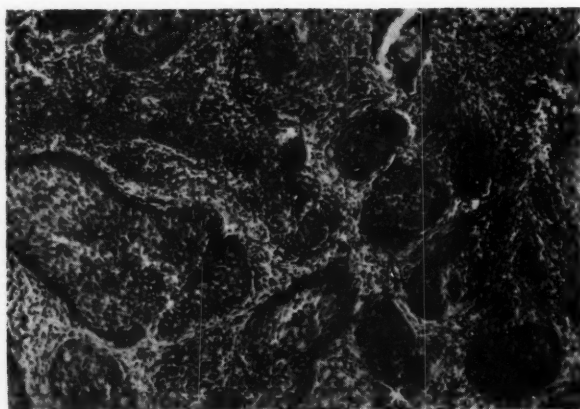


Fig. 1.—Epithelioma of cervix. (Neg. No. 272970-1, Armed Forces Institute of Pathology.)

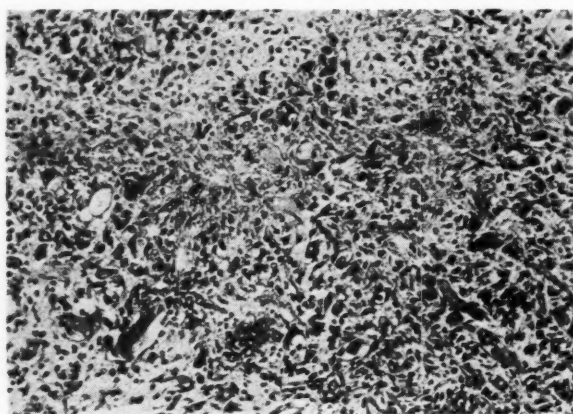


Fig. 2.—Sarcoma. (Neg. No. 272970-3, Armed Forces Institute of Pathology.)

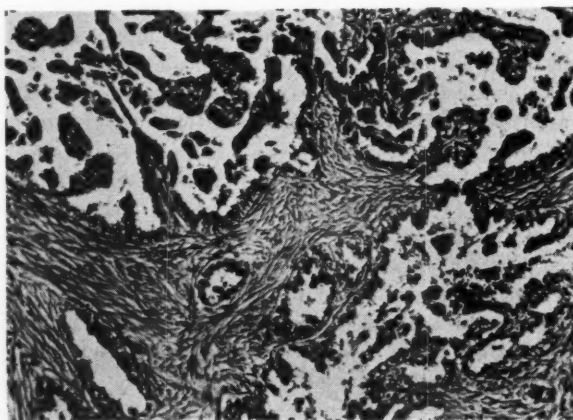


Fig. 3.—Adenocarcinoma. (Neg. No. 272970-2, Armed Forces Institute of Pathology.)

This cavity was lined by roughly nodular seminecrotic-appearing tissue and contained some blood clot. At the base of the specimen the tissue appeared torn and no cervical tissue was identified. (2) Several pieces of omental tissue, the largest measuring 16 by 6 by 3 cm. This tissue was indurated and contained nodules of firm, grayish-white tissue.

Pathological Report by Dr. G. R. Kerr: Sections taken from the margins of the large tumor growth of the uterus showed a sarcomatous type of neoplasm. The growth appeared predominately composed of spindle-shaped cells although many variations were present so that in many microscopic fields the pleomorphic structure was seen. In some areas there were frequent multinucleated tumor giant cells. There were many nuclear variations and mitotic figures were frequent. Many of the tumor cells were clustered about thin-walled blood vessels with areas of necrosis in the less vascular portions. Sections taken from the center of this tumor showed only necrosis and hemorrhagic infiltration. Sections taken from the tumor adjacent to the uterine lining also showed necrotic tissue with an infiltration of leucocytes replacing the endometrium.

Sections taken from the thinned-out uterine wall opposite the large tumor growth showed the endometrial lining replaced by adenocarcinoma. Irregular dark-staining neoplastic glands were present lined by immature epithelium. Purulent exudate was adherent to the lining in some places, and the uterine wall showed leucocytic infiltration. No evidence of sarcoma was found in these sections.

Pathological Diagnosis.—Sarcoma and adenocarcinoma of uterus; metastatic adenocarcinoma of omentum. (None of the present sections showed evidence of squamous-cell carcinoma, for which condition the patient was originally treated in 1941.) Sections of the indurated omental tissue showed adenocarcinoma infiltrating the tissue. The tumor here appeared rather similar to the adenocarcinoma found in the lining of the uterus.

The patient did fairly well for a short period, but expired approximately five weeks following surgery. Autopsy revealed these findings: The only tumor found in autopsy was metastatic adenocarcinoma. No evidence of sarcoma or squamous-cell carcinoma was found.

Anatomical Diagnosis.—Postoperative hysterectomy (with absence of uterus, tubes, and ovaries); marked abdominal adhesions producing obstruction of small intestine; marked ascites (approximately 12 to 15 L.); metastatic adenocarcinoma in aortic lymphatic chain and over peritoneum; moderate arteriosclerosis; moderate bilateral pulmonary congestion; broncho-pneumonia; moderate atrophy of breasts.

There is no doubt that this case represents an individual who was unfortunate enough to have three separate and distinct types of cancer, all primary in the generative tract, and probably arising from the uterus. That the site of the squamous-cell carcinoma was the cervix and that there was sarcomatous degeneration of a fibroid is clear; however, the origin of the adenocarcinoma cannot be proved. It seems reasonable to assume that the failure to find any ovarian tissue at operation or during autopsy, coupled with the history of previous extensive radiation therapy, would make the diagnosis of ovarian adenocarcinoma somewhat unlikely, and substantiate the fundal origin of the adenocarcinoma.

OBSTETRIC SHOCK DUE TO PULMONARY EMBOLI OF AMNIOTIC FLUID

COMMANDER ROY E. CROWDER (MC) USN, AND LIEUTENANT COMMANDER
E. S. BILLS (MC) USN, LONG BEACH, CALIF.

SINCE Steiner and Lushbaugh¹ first reported obstetric shock due to pulmonary emboli of amniotic fluid in 1941, several further reports have appeared in the literature confirming their finding and adding new facets to the syndrome. The condition is one of the most dramatic and tragic episodes encountered in pregnancy and labor. Steiner, Lushbaugh, and Frank,² in a recent communication, list the authenticated published cases.

While the number of authenticated cases is few, it is incumbent to report all such cases in which emboli composed of particulate components of the amniotic fluid are found in the lungs following sudden death in labor or post partum, so that some estimate of the frequency of the condition may be obtained.

The case here reported is somewhat different from those previously reported in that the patient had not been in labor and the elapsed time between the rupture of the membranes and death was only ten minutes.

C. L. H. (19508), a 28-year-old white woman, gravida ii, para i, had been seen regularly in the Prenatal Clinic since Jan. 31, 1949. She was last seen on Aug. 4, 1949, at which time she was apparently normal in all respects. Prenatal course had been uneventful throughout. Expected date of confinement was July 30, 1949.

Her husband stated that the patient was well until about ten minutes prior to admission when the membranes ruptured. She then said that she felt faint and collapsed, with frothing at the mouth and cyanosis. The husband was unable to obtain her pulse or heartbeat. He gave artificial respiration but obtained only a few gasps. He then brought her to the hospital in an automobile. When received at the hospital door at 9:10 P.M. no pulse, heartbeat, or respiration was obtained and she was pronounced dead.

She was immediately removed to the delivery room where an unsterile classical cesarean section was done and a 7 pound, 4½ ounce female infant was delivered at 9:14 P.M. Just prior to incision the fetal heart rate was 60 per minute and fairly strong. The baby appeared normal but did not breathe. The heart rate was 80 per minute but gradually slowed and stopped in spite of artificial respiration with oxygen in a respirator, Metrazol, 1 c.c., injected into the umbilical vein, and intracardiac Adrenalin, 1 mg. The stomach was aspirated and 15 c.c. of fluid obtained and the trachea was cleared with a catheter. The baby was pronounced dead at 9:35 P.M.

Necropsy findings in the mother showed essentially normal heart, liver, spleen, pancreas, adrenals, kidneys, and aorta. The right lung weighed 400 grams and was gray-red in color. The lung was normal in size and had a doughy consistency. Crepitation was almost absent throughout the lung. The cut surface was red in color and showed a small amount of froth. The bronchi contained a small amount of clear, viscid, colorless fluid. The vessels appeared normal. The left lung weighed 350 grams and was similar in appearance to the right lung. The uterus was large and measured 13 by 16 by 5 cm. There was an 8-cm. vertical, open incision of the anterior surface. The endometrial cavity contained decidual and fetal membrane. The Fallopian tubes were discolored red and otherwise appeared normal. The ovaries appeared normal.

Microscopic Examination.—Microscopic sections of the lung showed an intact thin pleura. The pulmonary alveoli contained small amounts of eosinophilic homogenous amorphous

material and in some areas, red blood cells. The outstanding change noted was marked dilatation of arterioles and capillaries. In many sections the arterioles contained emboli composed of amorphous debris, stringy material, and neutrophilic leucocytes. The amorphous debris contained some material that stained specifically with sudan IV for fat. The stringy material stained characteristically for mucin both in hematoxylin and eosin preparations and in thionine preparations for mucin. There was no evidence in the sections of acute inflammatory change of the bronchi, bronchioles, interstitial tissue, or pulmonary parenchyma. Section of the ovary showed a large corpus luteum with central fibrosis. A few large Graafian follicles were also seen. The ovary was otherwise congested. The uterus showed a small amount of decidual tissue attached to a hypertrophied, edematous myometrium. Another section showed a layer of trophoblastic cells overlying the decidua.

Anatomical Diagnosis.—Pulmonary embolism, amniotic fluid.

The clinical course and pathological findings in this case fit the clinical description of Steiner and Lushbaugh. Pregnancy had been normal and uneventful. The patient had been performing her household duties and felt well until the rupture of the membranes at term.

When the patient arrived at the hospital, heartbeat and respirations had ceased. Fetal heart tones were still present and post-mortem cesarean section was done within five minutes of the time of her arrival, and within fifteen minutes of the onset of the condition. There was no bleeding from the wounds, no evidence of hemorrhage within the abdomen, or externally. The findings in the lungs were typical. Careful examination of uterine vessels in the musculature around the cervix and in the corpus failed to reveal particulate components of the amniotic fluid.

The point of rupture of the membranes was at the external os but unfortunately no search was made for the site of point of entrance of the amniotic fluid.

We wish to thank Captain J. L. Zundell (MC) USN, and Lieutenant (j.g.) R. J. Kleinhenz (MC) USN, for their pathologic study of this case.

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U. S. NAVAL HOSPITAL

DYSGERMINOMA OF THE OVARY

DONALD J. NENNO, M.D., BUFFALO, N. Y

(From the Department of Gynecology, Mercy Hospital)

HEREWITH is presented a case of a dysgerminoma of the right ovary which followed a rapidly fatal course.

The woman was a private patient of Dr. Howard A. Dennee, admitted to the gynecological service of Mercy Hospital; she was a well-developed, well-nourished, 52-year-old, white, married, para 0, gravida 0. Two months previous to admission, she began to notice a swelling in the lower abdomen which was slowly increasing in size. She complained of low back pain, and symptoms of nocturia; urgency and pressure on the bladder had become noticeable in the last two weeks. Three days prior to admission, the patient had a chocolate-colored vaginal discharge but no vaginal bleeding or spotting. Previous to admission, she had an x-ray study of the pelvis and abdomen which showed the outline of a mass in the lower abdomen.

Past history revealed that for the last three years there had been episodes of left upper quadrant pain of a burning nature, which radiated through to the subscapular region. These pains lasted for periods of one to two weeks, but then disappeared for indefinite periods of time. The patient had had an appendectomy fifteen years ago, scarlet fever as a child, and pyelonephritis two years previously. She had a normal menstrual pattern with involuntary sterility, followed by menopause three years before admission.

She was admitted to the hospital on June 22, 1948, with a diagnosis of a large ovarian cyst. Physical examination revealed an elderly, well-developed, well-nourished, white woman, not acutely ill. Heart and lungs were not remarkable. The abdomen had the swelling of about a six months' pregnancy. The mass was in the lower abdomen and had a smooth outline. It was freely moveable in a range of a few inches with minimal tenderness. There was no free fluid in the abdomen or edema of the extremities. Vaginal examination was not helpful except to identify further a space-filling mass.

On June 24, 1948, at laparotomy under spinal anesthesia, a football-sized mass was found to replace the right ovary. The tumor was removed. The remaining ovary appeared grossly normal. There were no lymph nodes palpable and the bladder and the bowel were not remarkable. The postoperative course was uneventful. The patient was discharged on July 5, 1948.

Grossly, the tumor was made up of spongy tissue with cystic, necrotic areas, varying in size from an orange to a plum. The solid portion of the tumor was a plaque of dense reddish-purple tissue which cut with a rubbery consistency.

Microscopic examination showed a malignant primary ovarian tumor whose pattern was that of irregular masses and cords of epithelium-like cells separated by vascular trabeculae. The epithelium-like cells were fairly uniform in size, with clear, sharply demarcated cytoplasm. The nuclei, however, were distinctly atypical and hyperchromatic, and mitotic figures were common. The fibrous trabeculae were infiltrated by abundant lymphoid cells. There was extensive coagulation necrosis throughout the tumor. The impression was anaplastic dysgerminoma of ovary.

Two weeks after discharge, the patient began to have episodes of hemoptysis with a small amount of blood. An x-ray film of the chest revealed a mass in the left side of the chest suggestive of metastatic tumor. She was referred to the Roswell Park Memorial Institute for further therapy. She was bronchoscoped on Sept. 28, 1948, and the biopsy specimen obtained showed a tumor of the same configuration as noted in the ovarian tumor.

The patient was given radiation therapy to the left side of the chest and over the tumor site from various ports, totalling 3,624 r over a period of sixty-seven days. X-ray films of the chest showed little change in tumor size but some clearing of a left lower lung atelectasis.

The patient expired following uremic coma on Dec. 20, 1948. Necropsy showed metastatic involvement of the left lung, kidneys, liver, adrenals, left ovary, and right ovarian adnexa.

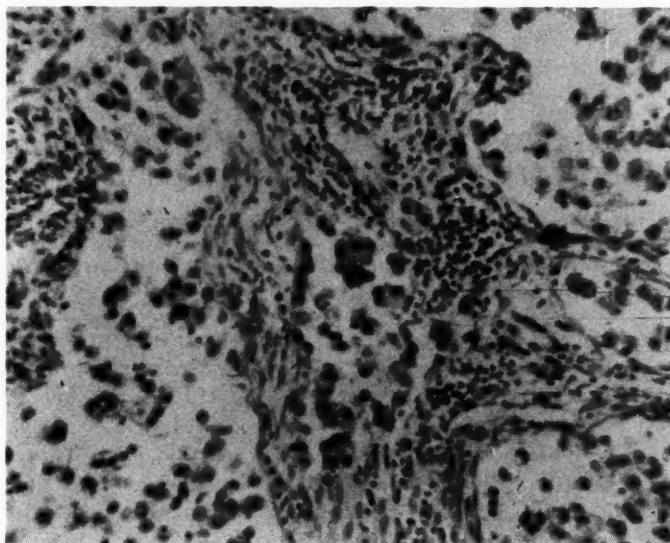


Fig. 1.—Lung metastasis showing fibrous trabeculae with lymphoid tissue in trabeculae. ($\times 100$.)

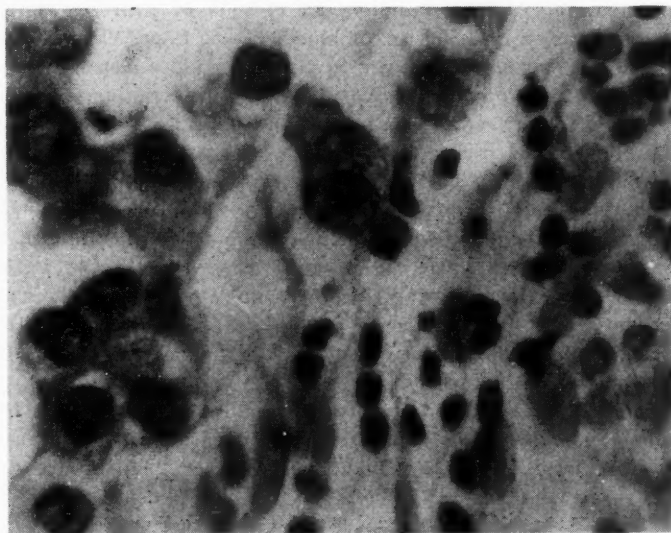


Fig. 2.—Lung metastasis showing typical cells of tumor. ($\times 430$.)

Summary

Despite the patient's involuntary sterility, there were no physical findings to substantiate a condition of hypoplasia of the gonads as the early case reports attempted to stress. This case, however, serves to emphasize that dysgerminoma does occur in the older-age groups and can behave in a biologically highly malignant fashion.

Although a rare condition, metastatic lesions in the lung should not be disregarded as a possible complication, and the x-ray therapy should include the mediastinal field in cases at all doubtful.

56 EDGEWOOD AVENUE

PELVIC EXENTERATION FOR ADVANCED UNCONTROLLED CANCER OF THE CERVIX WITH PRESERVATION OF COITAL FUNCTION

RAYMOND J. SIMMONS, M.D., ROCHESTER, N. Y.

(From the Department of Obstetrics and Gynecology, University of Rochester School of Medicine and Dentistry)

PELVIC exenteration for far-advanced cancer of the cervix uteri, recurrent and uncontrolled, as described by Brunschwig,^{1,2} is now a recognized procedure, though not widely practiced. Since July, 1948, the author has been doing this operation, and a case of unusual interest is herein reported.

Mrs. M. H. (No. 104419) is a 36-year-old white married para ii, gravida ii who was first seen on Sept. 25, 1948, with a five months' history of leucorrhea, postcoital bleeding, and occasional metrorrhagia. The cervix and upper vagina were replaced by a 5 by 6 cm. mass of fungating tissue with a hollowed-out crater in the mid-portion. The pelvic structures were freely movable except for fixation in the left lateral fornix. Papanicolaou smear showed Grade IV malignant cells and biopsy revealed adenocarcinoma of the cervix uteri. Immediately after admission, an episode of profuse vaginal bleeding occurred, requiring transfusion of 1,500 c.c. of blood. From Sept. 30 to Nov. 5, 1948, the patient received 5,400 r of roentgen therapy in equally divided doses to right and left anterior, posterior, and lateral ports. On November 27, nine radium needles were inserted into the cervix (each 2 mg. of radium), a total of 1,800 mg. hr. being given by this method. On December 16, 56.4 mg. of radium in a T tube with 10 mg. of radium in each of two colpostats were administered for 65 hours, for a total dosage of 6,769 mg. hr. Clinically, the tumor showed remarkable regression. However, on March 21, 1949, a Papanicolaou smear showed Grade IV malignant cells and more induration was felt in the base of the left broad ligament. On July 8, 1949, the patient was seen in the Out Patient Department after having three weeks of profuse vaginal bleeding. At that time she was found to have a completely frozen pelvis with a large rectovaginal fistula and intractable pain which prevented her from assuming a sitting or supine position. The question of more irradiation therapy arose, but was not considered safe. By Sept. 15, 1949, the patient had lost about thirty pounds, developed a 12 cm. rectovaginal fistula, and was being carried on around-the-clock opiates. She had several attacks of pyelonephritis, and rapidly went down hill with more weight loss and extreme inanition. On Oct. 2, 1949, a massive hemorrhage occurred from the rectal fistula and the patient almost bled to death.

On Nov. 4, 1949, Mrs. H. was transferred back to this clinic for terminal care, and was considered beyond all hope of any type of therapy.

A metastatic survey revealed no extrapelvic cancer. On Nov. 4, 1949, a total pelvic exenteration was done, using an abdominoperineal approach. The entire uterus, bladder, rectum, anus, rectosigmoid, and pelvic glands were removed *en bloc* without difficulty. Both ureters were implanted into the sigmoid by the Nesbit technique, and the wet colostomy was brought out at the level of the umbilicus, which was excised. The entire mass was removed perineally. The perineal wound could not be closed because of the complete absence of any soft tissue in this area. Instead, several gutta-percha drains were brought down, and these were removed within a few days. Postoperatively, the patient's course was completely afebrile and uneventful. She was discharged three weeks later with a Pierce bag. After discharge, she regained her normal weight within

three months. Mrs. H. has been completely free from pain, and the management of the wet colostomy has not been difficult. It has been noted on the patient's return visits to the clinic that the perineal wound had epithelized and formed an excellent functioning artificial vagina.

It is felt that the results in this case are particularly gratifying, especially in view of the fact that the pathological sections of the pelvic mass revealed extensive irradiation necrosis without any active cancer, a not uncommon finding in this type of case. This patient should survive for an indefinite period of time, living a fairly normal life.

Summary

A case of pelvic exenteration for far-advanced cervical cancer is presented as being of special interest due to the presence of a functioning artificial vagina created at operation. It is suggested by the author that the perineal wound be treated in a similar manner in subsequent cases.

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Department of Reviews and Abstracts

Selected Abstracts

Cancer, Malignancies

Olesen, H., and Albeck, V.: Primary Tubal Carcinoma, Acta obst. et gynec. Scandinav. 29: 246, 1949.

From the literature, the authors collected 479 reported cases of primary carcinoma of the Fallopian tube, and add one of their own, in a 47-year-old woman who had metastases in endometrium and mesovarium. This tumor constitutes from 0.1 to 0.5 per cent of genital cancers, and is most often found between the ages of 40 and 60 years. It was bilateral in one-third of reported cases; and it was most often located in the middle or distal thirds of the tube. The microscopic pattern may be papillary or adenomatous, and it may sometimes be erroneously diagnosed in cases of tuberculous salpingitis. The tumor is highly malignant in behavior, metastasizing promptly to peritoneum, omentum, uterus, ovaries, and regional lymph nodes. Endometrial metastasis, seen in the author's case, is unusual. About half of the patients had some menstrual irregularity, and one-fifth complained of leucorrhea alone. Hysterosalpingography may be of diagnostic aid. Of the 479 reported cases, only 12 five-year survivals were encountered. Treatment has usually been surgical, though some writers have recommended a combination of surgery and irradiation.

DOUGLAS M. HAYNES

Cesarean Section

Belouoschkin, B.: Extraperitoneal Cesarean Section as a Method of Operative Delivery in Infected Labor, Acta obst. et gynec. Scandinav. 29: 1, 1949.

Twenty-two instances are reported of extraperitoneal cesarean section performed in cases of infected labor in which absolute indication for section existed independent of the infection. Labor preceding operation was found to simplify the technical problem by stretching the lower uterine segment, thus facilitating reflection of the peritoneal flap. Endometritis and wound infection with secondary healing were routinely encountered postoperatively. Longitudinal primary abdominal incision was found to heal more readily than transverse. The uterus was usually opened by a crescent-shaped incision in the isthmus. One patient successfully tested the uterine incision by an uncomplicated spontaneous delivery 20 months following extraperitoneal section. There were two maternal deaths, one from acute yellow atrophy of liver, and one following septic femoral thrombophlebitis. There was one postoperative vesicovaginal fistula. Two infants were anoxic at delivery and could not be resuscitated. Four cases of repeat extraperitoneal section presented no special technical problem.

DOUGLAS M. HAYNES

Gynecology

Kleitsman, R. J.: Contribution to the Knowledge of Ovarian Leiomyomas, *Acta obst. et gynec. Scandinav.* 29: 161, 1949.

Among 682 ovarian tumors observed during the period 1931-1945, the author found only one case of leiomyoma. Pure ovarian myoma has been reported 17 times in the literature. There were coexistent uterine leiomyomas in 38.9 per cent of the group.

Ovarian myoma occurs most commonly in the decade from 30 to 40 years. The tumors are usually unilateral, and cannot be clinically differentiated from fibromas. Their myomatous character is determined by the use of special staining methods.

The histogenesis of ovarian myoma is thought to be from bundles of smooth muscle which may be found in the ovaries of newborn infants, beginning in the mesovarium and hilum between the ovarian vessels. Another less-favored theory suggests that they may originate from the smooth muscle of the ovarian blood vessels. It is thought that smooth muscle aggregates in the ovary may possibly be stimulated to tumor formation by hormonal irregularity, especially by ovarian hyperfunction.

DOUGLAS M. HAYNES

Kleitsman, R. J.: Contribution to the Pathologic and Clinical Features of Theca Cell Tumors, *Acta obst. et gynec. Scandinav.* 29: 175, 1949.

In his series of 682 ovarian tumors, the author encountered 2 examples of thecoma, and collected 84 other cases from the literature.

These tumors are made up of cells having a high lipid content, and resembling cells of the theca interna. They vary in gross size, occasionally growing as large as a man's head. They are solid in consistency and are characteristically yellow in color.

The age of occurrence is usually after 50 years, 3 patients were under 20, including one of the author's; the oldest reported patient was 92.

Clinically the tumors may produce irregular bleeding or pressure effects. Uterine myomas, adenomyosis, and endometrial hyperplasia are often associated. The tumors are usually benign. Only three instances of sarcomatous change have been reported. The treatment is surgical. X-ray castration was ineffectual in arresting growth of the tumor in the one case in which it was used.

DOUGLAS M. HAYNES

Kleitsman, R. J.: On the Problem of Ovarian Fibroma, *Acta obst. et gynec. Scandinav.* 29: 234, 1949.

In a series of 682 ovarian tumors observed from 1931 to 1945, there were 9 fibromas, an incidence of 1.32 per cent. Two were bilateral. Two of the patients had associated ascites, but none presented Meigs' syndrome (found in 25 to 45 per cent of cases reported by others). Most of the cases occurred between the ages of 31 and 40 years. Five patients had associated uterine leiomyomas. The tumors are usually small and are pedunculated in about 15 per cent of cases. The histolytic picture is characterized by either a diffuse stromal hyperplasia, or by circumscribed neoplasm adjacent to normal ovarian tissue. Circulatory disturbances are fairly common, but sarcomatous degeneration is reported in only about 1.5 per cent of fibromas, and no such case was observed by the author. Parity is not related, but concomitant pregnancy is uncommon. The tumors are believed to originate from the ovarian stroma. The treatment is entirely surgical.

DOUGLAS M. HAYNES

Harry Sered, Frederick H. Falls, and Bruce P. Zummo: Streptomycin in Gynecologic Tuberculosis, *J. A. M. A.* 142: 547, 1950.

The authors report 16 cases of genitoperitoneal tuberculosis. These patients were subjected to streptomycin therapy for six to eight weeks, operated upon, and given an-

other three-week course of treatment postoperatively. The dosage was 0.5 Gm. of drug twice daily. All patients showed some signs of clinical improvement during the pre-operative phase and the use of the drug preoperatively made the surgical procedure less formidable. Total hysterectomy and bilateral salpingo-oophorectomy are advised wherever ovaries are involved, with primary closure of the vagina and abdominal wall. Twelve of the 16 patients had tuberculous involvement of the endometrium even with negative endometrial biopsies.

The greatest incidence of genital tuberculosis occurs in the childbearing period. The average age of the patients was 26 years. Fourteen patients were Negro and two were white and the majority were parous women.

WILLIAM BERMAN

Labor, Complications, Management

Timonan, Sakari: Multiple Cartilaginous Exostoses in Connection With Labor, Acta obst. et gynec. Scandinav. 29: 138, 1949.

A case of obstructed labor consequent to pelvic deformity from hereditary chondrodysplasia is reported. The obstruction was caused by an exostosis at the puboileal junction which was not discovered until late in labor. The child, delivered by cesarean section, succumbed on the fourth day of life from cerebral hemorrhage secondary to a tear of the tentorium cerebelli. In this disease, cartilaginous exostoses of obstetric importance may be found on the iliac crest, the pubic crest, the sacrum, the sacroiliac synchondrosis, and the region about the hip joint, the ultimate result being an irregular narrowing of the pelvis. The author recommends careful prenatal roentgen studies of the pelvis in all patients with cartilaginous exostoses elsewhere, and cesarean section when an obstructing tumor is demonstrated.

DOUGLAS M. HAYNES

Pihlmaa, Aatos: On Acquired Vaginal Atresias, Resultant Parturition Difficulties and Treatment, Acta obst. et gynec. Scandinav. 29: 47, 1949.

Four cases of acquired vaginal atresia were observed as a complication of pregnancy at the I Women's Clinic of the University of Helsinki from 1936 to 1946. This represented 0.008 per cent of all obstetric cases, and 0.04 per cent of all gynecologic patients. It is pointed out that vaginal atresia is much more commonly acquired than congenital. Acquired atresias may be either longitudinal or transverse, the latter occurring more frequently. The atresia is most often found at the junction of the middle and upper thirds of the vagina, this point representing the line of division between the area supplied by the vaginal branch of the uterine artery and that supplied by the inferior vesical artery. The etiology of acquired vaginal atresia may be external violence (forceps delivery, prolonged spontaneous delivery, use of pessaries or of instruments designed to produce abortion, caustic chemicals); infections (typhoid, diphtheria or smallpox in children, puerperal infections in adults); sequelae of irradiation; and hormonal alterations of the vaginal mucosa (senile vaginitis). The commonest presenting symptom is difficulty with coitus. The diagnosis is made by the discovery on vaginal examination of a stricture; on aspiration old blood is obtained from a "retention tumor" (hematocolpos or hematometra). Complications of atresia with pregnancy include rupture of the uterus, bladder, cervix, and rectum, sequential fistulae, and cerebral hemorrhage in the infant. In the absence of pregnancy, there may be spontaneous perforation of a hematocolpos, or occlusion of an operatively opened hematometra with infection and pyocolpos or pyometra. Treatment of the nonpregnant patient consists of plastic operation to restore patency of the vagina. Operation is best not performed during pregnancy; incision or excision of the occluding membrane may be done at delivery if feasible, although cesarean section is most often indicated in these cases.

DOUGLAS M. HAYNES

Menstruation

Kaesser, Von O.: The Aetiology of Primary Amenorrhea, Gynaecologia 127: 220, 1949.

The author reports in detail ten cases of primary amenorrhea with emphasis placed on the differential diagnostic features of each. He recognizes two main classifications; pituitary failure and ovarian nonfunction.

In his own ten cases, five were probably pituitary in origin and two ovarian. The remaining three presented malformations of the uterus and vagina.

Two cases are presented in extreme detail pointing out the well-known classic differences between primary ovarian and pituitary amenorrheas. Although no endometrial biopsies or vaginal smears were done, the author did complete hormone determinations and extensive x-ray studies of the long bones and skull. The most striking changes were noted in the skull (small frontal sinuses and small sellae in pituitary dysfunction) and in the long bones of the hand which revealed retarded ossification in the pituitary group.

The general body types of these patients conformed to the x-ray findings. The differences in hormone findings, sugar tolerance tests, basal metabolism rates, etc., were not conclusive enough to warrant in themselves a diagnosis of either pituitary or ovarian failure.

Treatment (if the diagnosis can be made) is obviously replacement therapy.

EUGENE N. SCADRON

Newborn

Bryce, Lucy M., Campbell, Kate, Braydon, J. J., Jakobowicz, Rachel, and Kiel, Lorna: The Effect of Hetero-Specific Pregnancy on the Hemoglobin and Red Cell Levels in the New-Born Infant, M. J. Australia 2: 337, 1949.

Investigations by the authors show that in babies with ABO or Rh blood factors incompatible with those of their mothers the hemoglobin levels and color indices are lower than those in babies of the control group, whereas the red-cell counts are all almost identical in each group. It is usually assumed that the action of incompatible maternal blood factor antibodies on the fetal cells is hemolytic. It is postulated that there are two processes brought about by blood factor incompatibility which may act with detriment to the infant. The first of these is a process which inhibits normal utilization of iron. This process appears to predominate or to be the only one operative in cases of ABO incompatibility and in those cases of Rh incompatibility in which there are no demonstrable Rh antibodies in the maternal serum. Its effects may be so small that they are not always detectable in individual cases. The second process is the hemolytic one, which, when present, may give rise to such severe manifestations that the coexistent presence of the anti-hematopoietic element is masked. It is obvious that Rh incompatibility which has not resulted in demonstrable sensitization of the mother and the large majority of cases of ABO incompatibility between mother and child give rise to clinical effects which are very mild.

WILLIAM BERMAN

Genson, Clifford O., Penberthey, Grover C., and Hill, Edward J.: Hernia Into the Umbilical Cord and Omphalocele (Aminocele) in the Newborn, Arch. Surg. 58: 833, 1949.

The term omphalocele or aminocele should be restricted to those congenital defects in which there is herniation of the abdominal viscera into a sac covered by peritoneum and amniotic membrane through the umbilical and supraumbilical portion of the abdominal wall. In contrast, a hernia into the umbilical cord has a defect limited to the umbilical opening. The incidence of these conditions is about 1:6,000 births. It is essential that operative treatment be undertaken within a few hours after birth because there is a tendency for the amniotic sac to disintegrate or rupture with resulting peritonitis and subsequent fatal

outcome. In the case of omphalocele or aminocoele the authors stress the importance of two-stage closure in order to reduce the operative mortality. The presence of liver in the sac indicates a poor prognosis. Operative procedures and points in the operation are stressed to reduce the mortality. The authors point out that omphaloceles originate in the third week of embryonic life whereas hernia in the umbilical cord occurs in the eighth to tenth week.

WILLIAM BERMAN

Placenta

Abolius, J. A.: X-ray Examination in Cases of Placenta Previa, Acta obst. et gynec. Scandinav. 29: 150, 1949.

In the Norrköping Lying-In Hospital, during the period 1937-1948, indirect placentography was used 189 times in 172 patients. There were 47 instances of placenta previa, 26 of low implantation of the placenta, 23 of abruptio, and 148 of hemorrhages of varying degrees in pregnant women found not to have placental abnormality. The best results were in cases of placenta previa, with 31 correct diagnoses, 12 uncertain, and no wrong diagnoses. In low implantation of the placenta, there were 14 correct diagnoses, 11 uncertain, and no wrong diagnoses. Three cases later shown to be placenta previa were incorrectly diagnosed: 2 as unexplained subpartum hemorrhage, and 1 as abruptio placentae. The author recommends the use of placentography in all cases of vaginal bleeding after the sixth or seventh month.

DOUGLAS M. HAYNES

Pregnancy, Physiology

Szontagh, F. E.: Capillary Permeability, Serum Proteins and Hematocrit Values in Normal Pregnancy, Gynaecologia 127: 240, 1949.

The author's thesis is based on the fact that since plasma volume is increased in normal pregnancy and subnormal in toxemias, it may be therefore inferred that fluid escapes through the capillary walls. For these reasons investigations were done in the normal pregnant woman to determine the degree of capillary permeability.

The procedure of Landis was used, which is a method of compressing one arm of the subject (under a pressure of 40 mm. Hg for thirty minutes), removing a blood sample from the cubital vein, and comparing the hematocrit values with the blood sample removed from the free arm. Concentration of the serum proteins in each arm were also done and differences noted.

Results in twenty cases are reported. With the above procedure significant differences were obtained and in amounts to warrant the assumption of an increase of capillary permeability in normal pregnancy.

A high protein concentration of the capillary filtrate was definitely noted near term. Likewise it was found that the serum protein content and hematocrit values decrease in the course of pregnancy (substantiating facts previously known and discovered by other methods). It was concluded by the author that the decrease of proteins, observed by the Landis method, proves that the decrease is due to the albumin content of the capillary filtrate.

There are several complete tables illustrating the results and actual values found in each of the cases studied. An extensive bibliography is appended.

EUGENE W. SCADRON

Rosa, Pierre: Studies of the Interchange of Inulin Between Mother and Fetus, Acta clin. belg. 4: 169, 1949.

The author set out to determine the volume of amniotic fluid, using inulin and the dilution technique. In so doing he studied many of the factors which would vitiate the use of this procedure.

Inulin injected transabdominally through a spinal needle into the amniotic sac does not appear in the blood of the mother. Similarly, inulin infused intravenously into the maternal blood stream does not appear in the amniotic fluid except in one instance (an elderly overdue primipara with a difficult labor). After the injection of inulin into the amniotic sac inulin may be found in the fetal circulation at a variable time following the injection. Inulin injected into the amniotic sac of one fraternal twin does not appear in the amniotic sac of the other. Inulin injected into the amniotic sac of one identical twin does finally appear in the amniotic sac of the other.

These and other supporting data are taken to indicate that the normal fetus intermittently swallows amniotic fluid. When inulin is present it is absorbed from the bowel into the fetal circulation. It does not enter the maternal circulation or vice versa (except in an exceptional case, the one elderly primipara) but is excreted, in small amount, by the kidney and is then returned by micturition to the amniotic fluid.

The method used makes it possible to calculate the volume of the amniotic fluid (five values are given, range from 545 to 920 ml.) and the amount of amniotic fluid swallowed in a given time (no quantitative data presented).

It is concluded that inulin injected into the amniotic fluid follows the cycle: amniotic fluid—gastrointestinal tract—blood—urine—amniotic fluid; the formation of amniotic fluid is not a filtrate of either fetal or maternal blood; the amnion, the membranes, the fetal vessels of the placenta and funiculus are impermeable to inulin; the placenta is generally impermeable to inulin except following injury provoked by labor and postmaturity; a third circulation exists in identical twins; the quantity of amniotic fluid may be calculated in this fashion: fetal micturition occurs and the volume does not exceed 50 ml./24 hr.; it is possible to calculate the volume of amniotic fluid swallowed by the fetus (a detailed derivation of the formula for this calculation is presented, no data); the procedure could be used to determine fetal death except when certain fetal anomalies occur (no work done); this method combined with the determination of thiocyanate space and maternal inulin space could be used to calculate the fetal extracellular space (no work done); and the procedure described “n’ a provoqué le moindre trouble ni chez la mere ni chez l’enfant.”

ROY W. BONSNES.

Naeslund, J., Snellman, O., Csapo, A., and Erdös, T.: Studies on the Contractility of the Uterine Body, Isthmus and Cervix Under Normal Conditions, During Pregnancy, and in Labor *Acta obst. et gynec. Scand. 29*: 291, 1949.

The contractility of uterine muscle was studied by means of a technique based on the discovery that the proteins actin and myosin, isolable from the myometrium, may combine to form actomyosin, a new substance which is contractile in the presence of adenosine triphosphate (ATP). Sections from corpus and isthmus were taken from uteri obtained at hysterectomy, at hysterotomy for therapeutic abortion, and at cesarean section. When a stock solution prepared from myometrium, potassium chloride, and ATP was sprayed across the surface of a solution of potassium and magnesium chloride, actomyosin was deposited as a fine thread. The length of threads so obtained was measured with a micrometer, and then their contraction following the addition of 1 per cent ATP solution, such contraction being to some extent proportional to actomyosin content. By this method, nongravid myometrium showed a slightly greater contractility of the uterine body as compared with the cervix. The contractility of pregnant myometrium was increased; and the myometrium of the corpus during labor exhibited greatly increased contractility, whereas it was very slight in muscle from the isthmus.

Quantitative determinations of the actomyosin content of the same samples that produced the actomyosin threads were made, using a viscosity method. In nongravid

uterine muscle, the actomyosin content averaged 5 mg. per gram corporeal muscle, and 4 mg. per gram cervical muscle. During pregnancy, mean corporeal concentration rose to 8.5 mg., and isthmic content to 6 mg. In tissue taken during labor, the mean value for the body was 10.7 mg., while that for the isthmus was 3.9 mg., so that isthmic actomyosin concentration apparently drops toward the end of pregnancy.

The authors point out that the myometrium also contains a water-soluble compound, termed the X-factor by Csapo, and that this substance has a stimulating effect on the contractility of the actomyosin threads. The X-factor is thought to be an enzyme occurring only in uterine muscle. Its concentration increases during pregnancy, and is especially high in the muscle of the corpus uteri during labor.

The suggestion is made that the concentrations of actomyosin and of the X-factor may play some part in the initiation of uterine contraction.

DOUGLAS M. HAYNES.

Sterility, Contraception, Fertility

Calkins, L. A.: Reproduction in the Older Woman, J. A. M. A. 141: 635, 1949.

In an analysis of 5,186 deliveries in primiparas, and 4,687 deliveries in multiparas, special attention is given to the older age groups, i.e., primiparas 35 years old and over and multiparas 40 years old and over. The incidence of major complication was higher in the older group of primiparas than in the younger groups. The incidence of such complications was higher in multiparas 35 to 39 years of age and in those 40 years of age and over, than in younger multiparas, but no higher in the 40-year age group than in the 35- to 39-year age group. The complications that showed the highest incidence in the older age groups of both primiparas and multiparas were hypertensive cardiovascular disease and uterine myomas. The incidence of late toxemia of pregnancy was not higher in older primiparas than in younger primiparas. Cesarean section was done more frequently in the older age groups, both for primiparas and multiparas; this was due in part to the increased incidence of heart disease and uterine myomas in these age groups. But, in the older primiparas, cesarean section was done in some cases because of the fear that "something might go wrong" during labor in these patients; the author is now of the opinion, however, that the operation was not necessary in these cases. In uncomplicated cases in elderly primiparas and multiparas, the progress of labor was much the same as in the younger women in both groups. The fetal and neonatal mortality was higher in the older age groups, but this was due largely to increased operative interference and to the presence of fibroids. When pregnancy occurs in a woman over 35 years of age, a careful examination should be made; if no major complications are found, the obstetrician can undertake the care of these older patients "with the same confidence" as of younger patients.

HARVEY B. MATTHEWS.

Jones, G. E. Seegar: Some Newer Aspects of the Management of Infertility, J. A. M. A. 141: 1123, 1949.

In a group of 63 women with primary sterility and 35 with secondary infertility, without demonstrable anatomic pathological conditions, the ovarian status was evaluated by means of basal temperature readings, determination of urinary pregnanediol, study of cervical mucus, and endometrial biopsies. Inadequate corpus luteum function or progesterone metabolism was found to be more common than defects of the follicular phase and disturbances of ovulatory mechanism. The endometrial biopsy showed inadequate progesterone stimulation in the largest percentage of cases, while the pregnanediol excretion was less frequently below normal; this indicates that endometrial dysfunction, or a failure of the endometrium to respond to progesterone stimulation is not an infrequent cause of sterility. Treatment included methods to correct underlying defects, chiefly

borderline thyroid defects and nutritional deficiencies (including vitamin E), rarely other endocrine deficiencies. In some cases oral progestogen was used in a cyclic manner during the luteal phase, when there was corpus luteum deficiency. Estrogen was used in the form of suppositories in cases where the cervical mucus was abnormal, with no other pathologic conditions. In patients with anovulatory cycles, cyclic estrogen-progesterone therapy was used. Pituitary gonadotropin was used in 3 cases in which there were anovulatory cycles of normal or shorter than normal duration. Of 60 women adequately treated by these various methods and followed up, 21 have given birth to living infants and 7 others are now pregnant. Since, in this series, most of the patients have not shown a single deficiency and all deficient factors have been treated as indicated by the study of each patient, it is difficult to evaluate treatment scientifically.

HARVEY B. MATTHEWS.

Toxemia

Hipsley, Eben H.: Some Aspects of Nutrition as Related to the Practice of Obstetrics and Gynecology, M. J. Australia 24: 775, 1949.

The author points out the importance of diet in the practice of gynecology and obstetrics. There are some interesting observations made on the etiology of toxemia of pregnancy. Toxemia is much less common among New Guinea natives than among civilized Australians. Eclampsia in Australia is more common from May to September than from January to March. The peak month for eclampsia corresponds with the lowest value for vitamin C consumption. As a result of dietary surveys overseas and in Australia, toxemia of pregnancy has been statistically associated with poor diet groups. An examination of the evidence has suggested examination of the level of magnesium in the diets of normal and toxemic women. The symptoms, signs, and pathology of experimental magnesium deficiency in animals are remarkably similar to those found in eclampsia; tonic and clonic convulsions, edema, albuminuria, and nephrosis-like kidney lesions. Bovine eclampsia closely resembles human eclampsia. It is invariably associated with very low serum and urinary magnesium levels.

WILLIAM BERMAN

Correspondence

Note on the Cyclical Changes of Cells of the Urinary Smears and Their Correlation to the Menstrual Cycle

To the Editor:

We want to correct a statement made by Drs. Paul F. McCallin, E. Stewart Taylor, and R. W. Whitehead, which appeared in the introduction of the paper, "A Study of the Changes in the Cytology of the Urinary Sediment During the Menstrual Cycle and Pregnancy," published in the July, 1950, issue of the JOURNAL: "Also, in studying urinary smears from non-pregnant women to establish a normal, we found cyclical changes that can be correlated with the menstrual cycle and this paper gives a preliminary report on these cellular changes." In *La semana médica*, 2: 867, 1946, *The Journal of Clinical Endocrinology* 8: 76, 1948, and *The Journal of Clinical Endocrinology* 9: 1362, 1949, we published papers on the subject, the first one (1946) in Spanish and the others in English, under the title "Cytological Cycle of the Urinary Sediment and Its Parallelism With the Vaginal Cycle." In 1948 and in 1949, in the paper, "Smears From the Female Urethra and Their Relationship to Smears of the Urinary Sediment," we summarized the findings previously published in the 1946 and 1948 papers as follows:

1. The cells present in the urinary smear, when this sediment is smeared, fixed, and stained by Shorr's technique, are very similar to, but not identical with, the vaginal cells.
2. These cells, contrary to what can be supposed, are not vaginal cells washed out by the urinary stream.
3. The cytological content of the vaginal and of the urinary sediment, taken simultaneously from the same patient, show a striking similarity: each one undergoes the same morphological and staining changes in relation to the absence, normal presence, or therapeutic administration of estrogens.

Furthermore, studies were performed and striking differences were found in the urinary smear of normal preadolescent girls, normal adult women (in whom daily changes can be observed during the menstrual cycle, including the sharp intermenstrual increase and decrease of cornified cells), in menopausal women, in primary and secondary amenorrhea, and in smears of men and boys. The effects of estrogen, androgens, and progesterone were also studied, this latter one being the subject of a paper at the present moment in press.

ENRIQUE B. DEL CASTILLO, M.D.

MONTEVIDEO 117
BUENOS AIRES
ARGENTINA

Reply by Dr. Taylor

To the Editor:

In reply to Dr. Castillo, the work described in our paper, "A Study of the Changes in the Cytology of the Urinary Sediment During the Menstrual Cycle and Pregnancy," published in the July, 1950, issue of the JOURNAL, was done in 1948 and the early part of 1949. At that time volumes of the *Index Medicus*, which were our source for reviewing the literature,

did not contain references to Dr. Castillo's studies. The earliest mention of his 1946 paper in *La semana médica* was in the 1947 *Index Medicus*. This was not available to libraries until late 1949 (after our paper had been submitted to the JOURNAL).

In reviewing Dr. Castillo's papers, we find that his studies do not parallel the work reported in our paper. He has studied voided urine and emphasizes that the cells he examined are from the anterior urethra, while our method of examining catheterized urine rules out the presence of such cells. Also, he does not differentiate between the actual proliferative and secretory phases of the menstrual cycle but mentions only the variation of the urinary epithelium in the presence or absence of estrogen, i.e., preadolescent, adult female, and postmenopausal stages. No mention is made of the effect of pregnancy or progesterone upon urinary sediment in Dr. Castillo's published papers. We have also used the Shorr stain but have not found it to give sufficient cellular detail to reveal the variations during the menstrual cycle.

In the original thesis we noted the study of Biot and Beltran in *La semana médica* 51: 532, 1944, in which they reported that by counting the number of epithelial cells in voided urine they found an increase in the number of desquamated cells at the time of ovulation. Because of the use of voided urine and the absence of morphological and staining studies we did not feel their work was pertinent to mention in our published abstract. Also, we are now aware of the paper by Wasserman in *Comptes rendus des séances de la Société de biologie* 142: 322, 1948, who reported a marked increase in the desquamation of urinary epithelial cells 4 to 8 days prior to menstruation but not at midcycle. With this finding our reported work is in agreement.

Prior to Dr. Castillo's earliest paper, in November, 1946, noting the effect of estrogen upon the epithelium of the urinary tract, Papanicolaou noted these changes (*J. A. M. A.* 131: 372, 1946). Dr. Papanicolaou's paper is given due credit in our bibliography. However, the dates of these publications indicate that these observations were made independently. Our work has rather been an extension of these observations in that the combined effect of estrogen and progesterone has been studied both during the menstrual cycle and pregnancy.

E. STEWART TAYLOR, M.D.

PAUL F. MCCALLIN, M.D.

RICHARD W. WHITEHEAD, M.D.

4200 EAST NINTH STREET

DENVER, COLO.

OCT. 27, 1950

Item

American Board of Obstetrics and Gynecology

The next scheduled examination (Part I), written examination and review of case histories, for all candidates will be held in various cities in the United States and Canada on Friday, Feb. 2, 1951. Arrangement is being made for proctors in locations convenient to the candidates' places of practice.

Candidates who have already successfully completed Part I and who desire to reopen their applications for Part II examinations may do so by notification to this office until Feb. 2, 1951.

The next oral and pathology examination (Part II) will be held at The Waldorf-Astoria Hotel, New York City, from May 10 to 16, inclusive, 1951.

For new Bulletins or other information address:

PAUL TITUS, M.D., Secretary
American Board of Obstetrics and Gynecology
1015 Highland Building
Pittsburgh 6, Pa.

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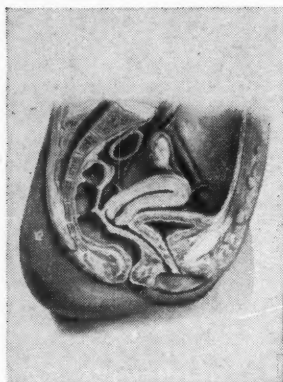
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Not just milk replacement but casein replacement...

Casein—and also lactalbumin—are frequently the cause of hypersensitivity to cow's milk. This hypersensitivity can be manifested by gastrointestinal upsets followed in time by eczema of a mild or acute nature. In such cases cow's milk of all types must be eliminated from the diet. Mull-Soy is a near equivalent for milk to be used in these cases.

NSB

A scientifically sound formula for avoidance of casein allergy
 Stable—vacuum packed
 High in unsaturated fatty acids essential for growth
 Pleasant-tasting
 A homogenized liquid, not a powder or a hydrolysate
 For hypoallergenic diet in infants or adults look to

MULL-SOY®

The Borden Company
 Prescription Products Division
 350 Madison Avenue, New York 17



At drugstores in 15½ oz. tins.

Mull-Soy diluted with equal volume of water

Average whole cow's milk

Calories per fl. oz.	20	20
Protein	3.1%	3.3%
Fat	4.0%	3.8%
Carbohydrate	4.5%	4.9%
Total Minerals	1.0%	0.7%
Water	87.2%	87.3%

